SYMPOSIUM ON SURGICAL LESIONS OF THE THYROID

Vol. 16 NOVEMBER, 1944 No. 5

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

EDITORS

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CONTENTS

Symposium on Surgical Lesions of the Thyroid

Diffuse and Adenomatous Goiter and Goiter Induced by Various Agents. Albert C. Broders, M.D., and Edith M. Parkhill, M.D., Rochester, Minn. ---- 633

Diagnosis of Thyrotoxicosis. Willard O. Thompson, M.D., Chicago, Ill. ---- 647

The Heart and Circulation in Patients With Hyperthyroidism. Robert W. Keeton, M.D., Chicago, Ill. ---- 657

The Medical Management of Thyrotoxicosis. David P. Barr, M.D., New York, N. Y. ---- 668

Chemotherapy in Hyperthyroidism. E. B. Astwood, M.D., Boston, Mass. ---- 679

Factors Influencing Operability and Mortality Rate in Goiter. Warren H. Cole, M.D., Chicago, Ill. ---- 688

Anesthesia in Thyroid Surgery. R. Charles Adams, M.D., and Claude F. Dixon, M.D., Rochester, Minn. ---- 700

Technique of Thyroidectomy. Frank H. Lahey, M.D., Boston, Mass. ---- 705

Drainage in Thyroidectomy. Donald Guthrie, M.D., F.A.C.S., and Irwin Schimmel, M.D., Sayre, Pa. ---- 725

A New Plan in the Operative Treatment of Patients With Severe Hyperthyroidism. Major Charles E. Rea, Medical Corps, A.U.S. ---- 731

The Management of Postoperative Complications in Thyroid Surgery. Howard M. Clute, M.D., Francis R. Kenney, M.D., and Burton E. Hamilton, M.D., Boston, Mass. ---- 739

The Problem of Thyroid Crisis. Robert W. Buxton, M.D., Ann Arbor, Mich. ---- 748

Goiter in Children. John deJ. Pemberton, M.D., and B. Marden Black, M.D., Rochester, Minn. ---- 756

Goiter in the Southern States. Howard Mahorner, M.D., New Orleans, La. ---- 764

Thyroiditis. Nathan A. Womack, M.D., St. Louis, Mo. ---- 770

Malignant Goiter. Robertson Ward, M.D., San Francisco, Calif. ---- 783

Parathyroid Tetany. Cyril M. MacBryde, M.D., St. Louis, Mo. ---- 804

Editorial

Progress and Future in the Treatment of Goiter. Warren H. Cole, M.D., Chicago, Ill. ---- 811

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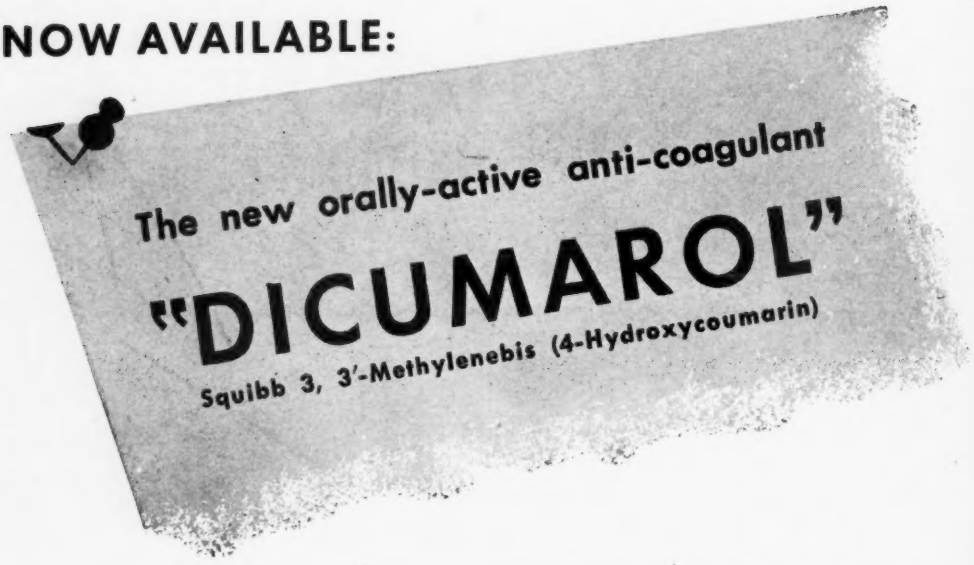

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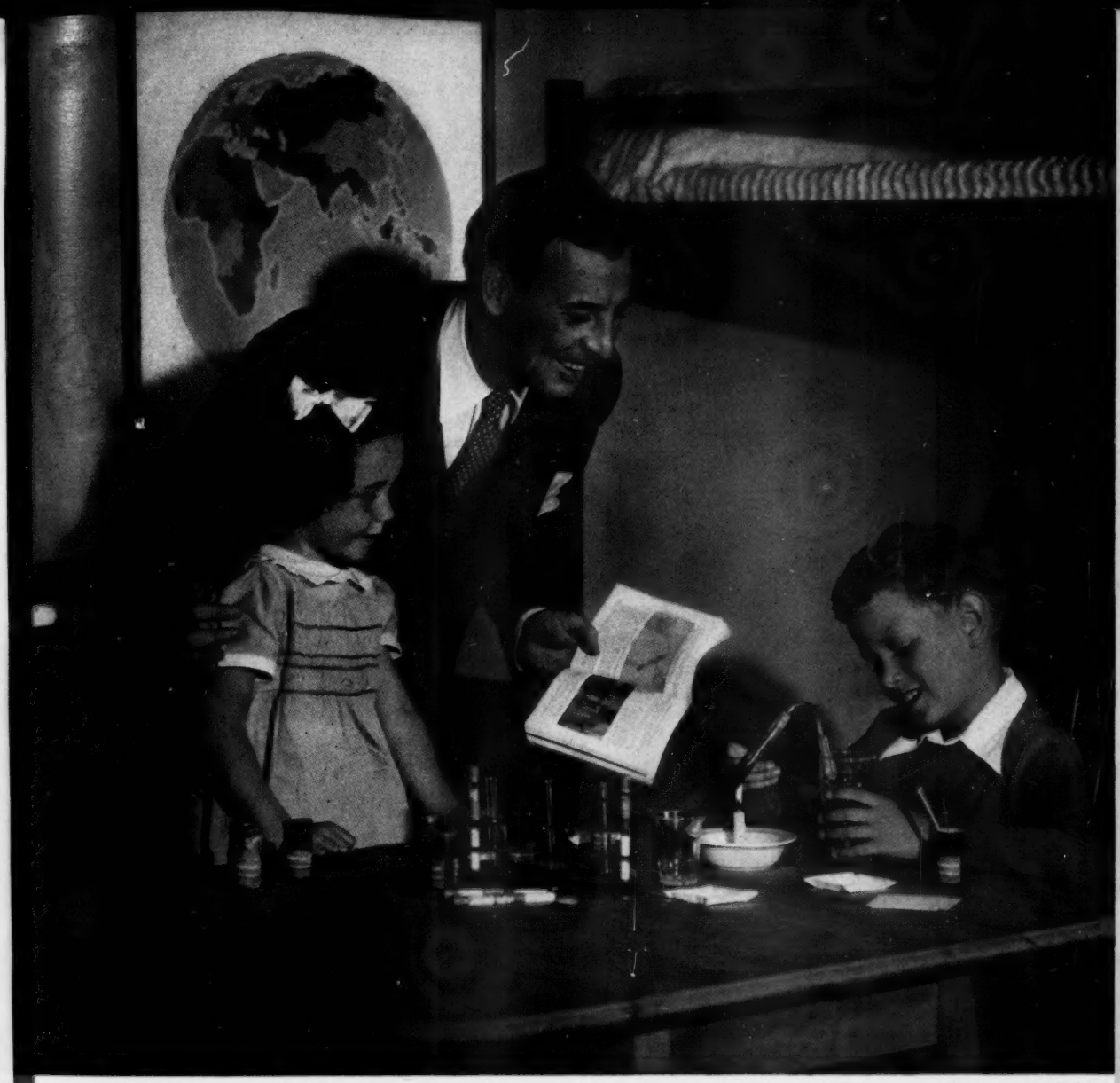

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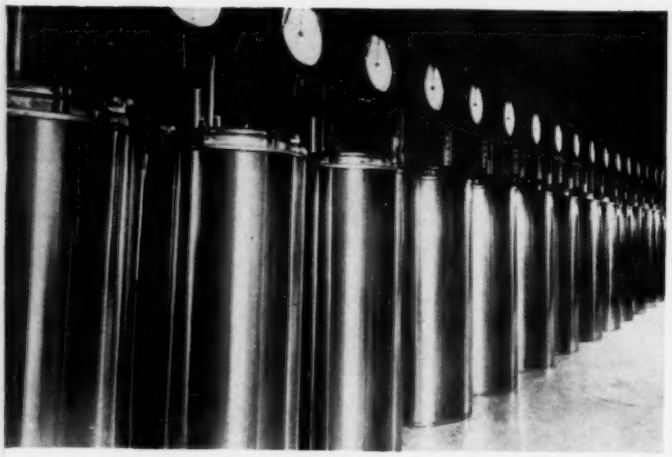

(Above) D&G research developments in the field of high heat sterilization have led to the elevation of temperatures in the processing of both boilable and non-boilable catgut. D&G has applied this knowledge to the design of special equipment for the precise control of every phase of the sterilizing operation.

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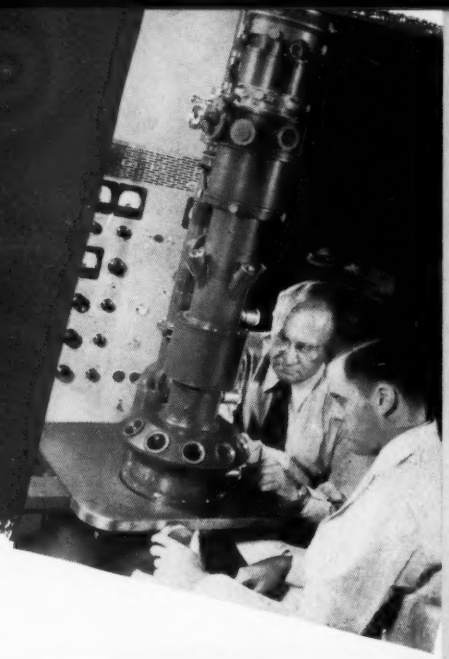
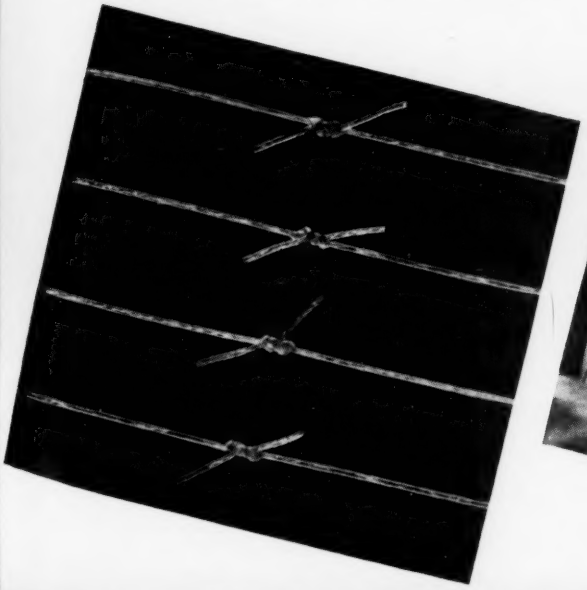


(Above, right) **D&G facilities for the study of physical properties of sutures include one of the largest general research laboratories fully equipped with the most modern devices for electron microscopy, ultraviolet and infrared photomicrography and other forms of specialized research.**

(Right) **The finest facilities for studies in all branches of chemistry have enabled D&G research to establish the high degrees of blandness and neutrality for which D&G sutures are noted. Likewise, procedures for exacting control of these qualities in production are important steps in suture manufacturing routine at D&G.**

(Below, right) **D&G research activities include the most modern facilities for experimental and clinical research. Out of this work have come many important contributions to practical knowledge of the behavior of sutures and new developments in suture materials which have done much to advance surgical facility.**

(Below) **D&G studies of physical properties of sutures have made possible higher standards of tensile strength and improved procedures of surface finishing. The D&G Matte Finish provides a satin-smooth surface with sufficient traction to cause the strand to grip firmly on itself when knotted.**



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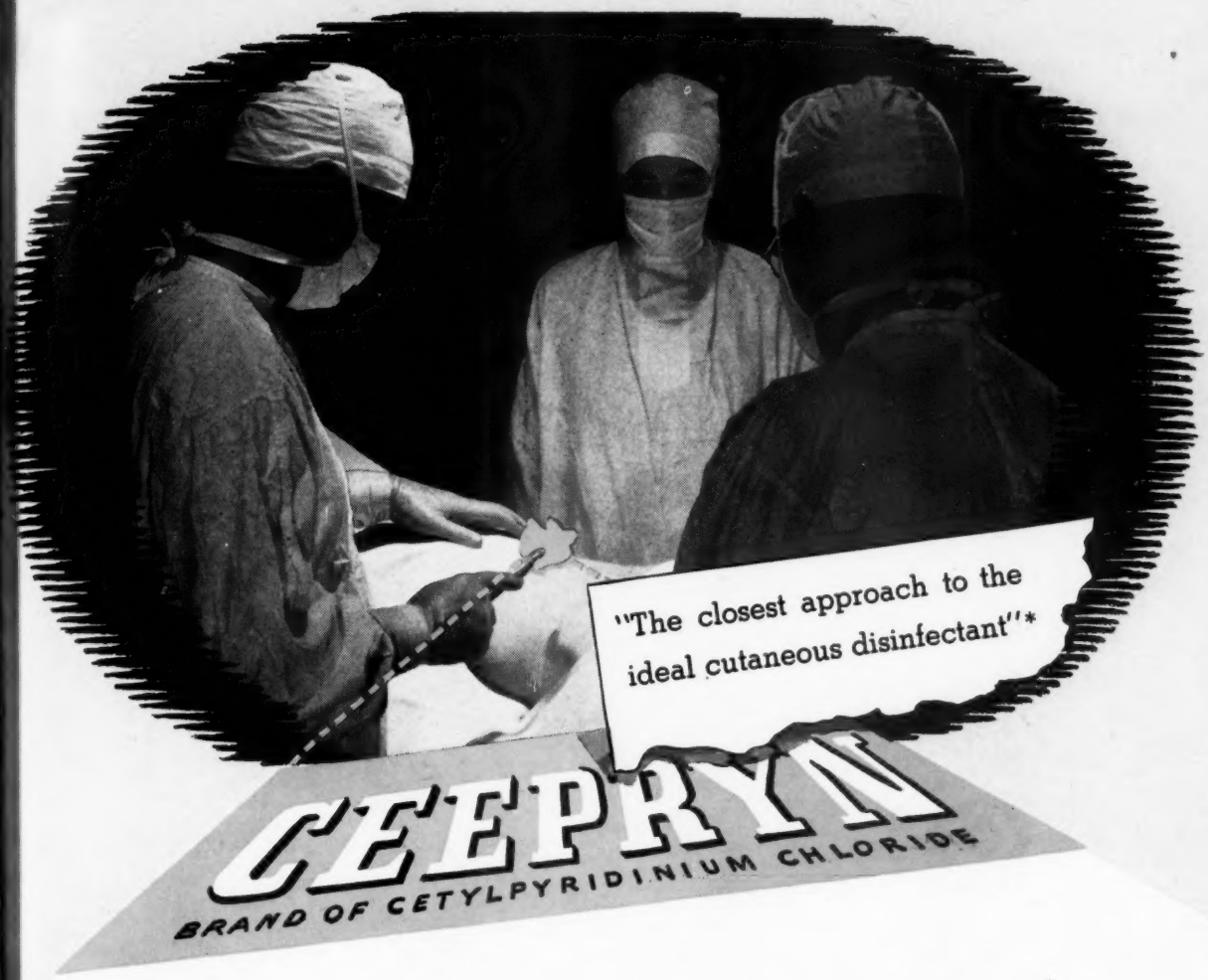

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*Kramer, G. B., and Sedwitz, S. H.: Ceepryn clinical and bacteriological studies, Am. J. Surg. 63:240-245 (Feb.) 1944.

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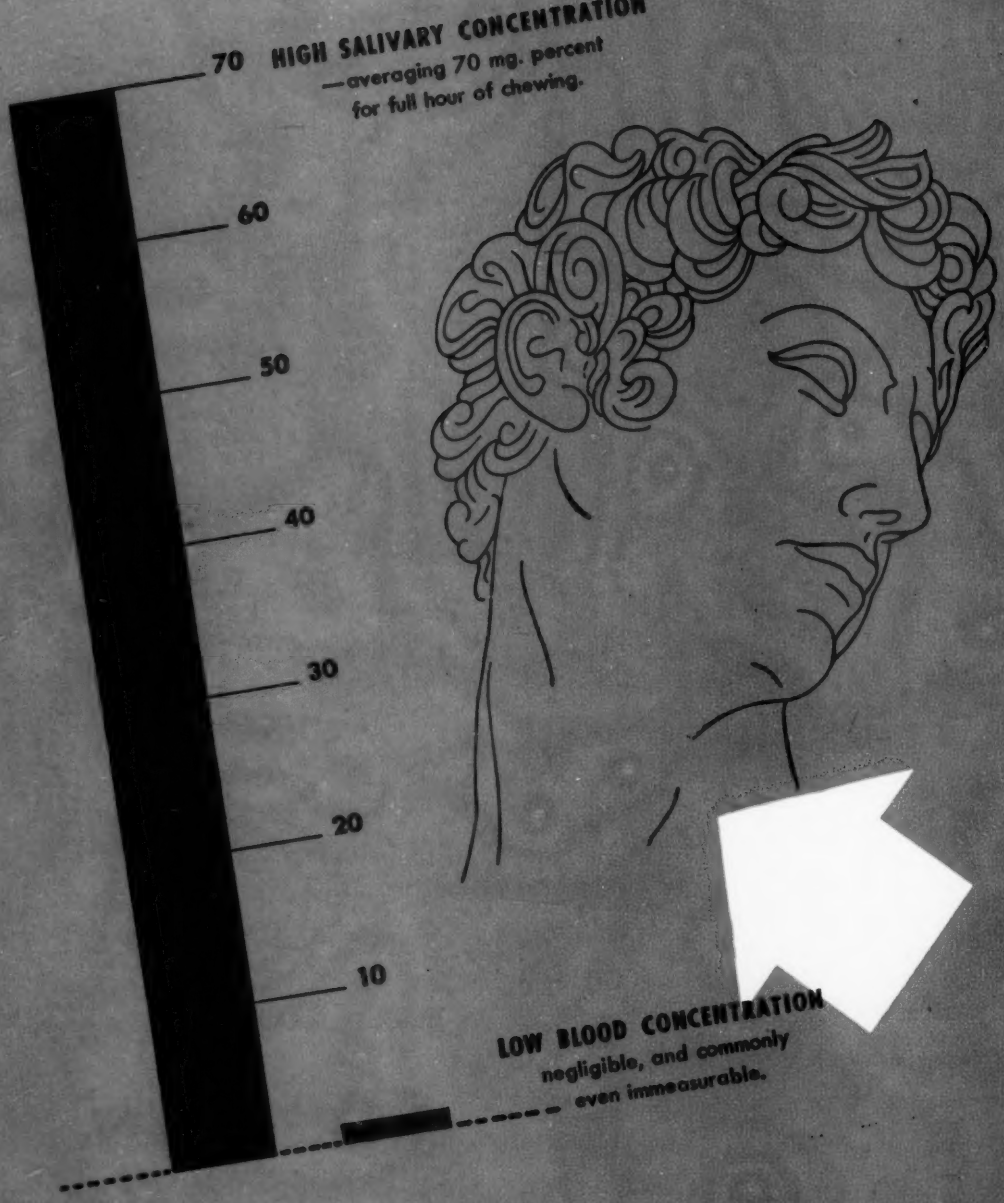
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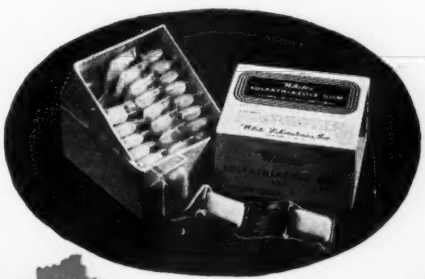

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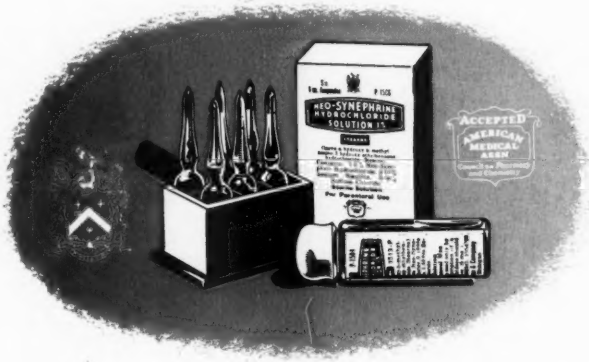

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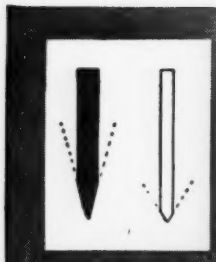

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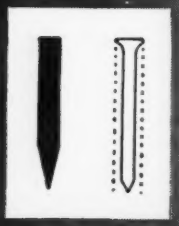

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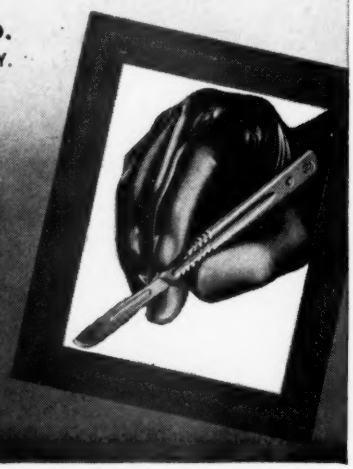

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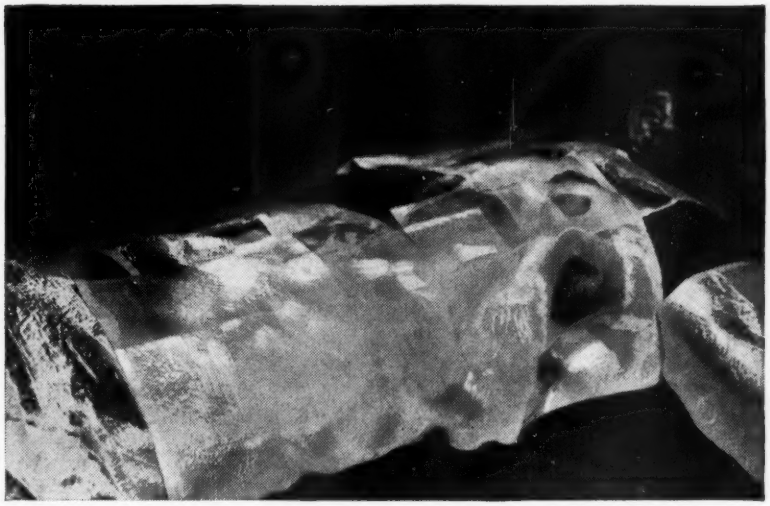

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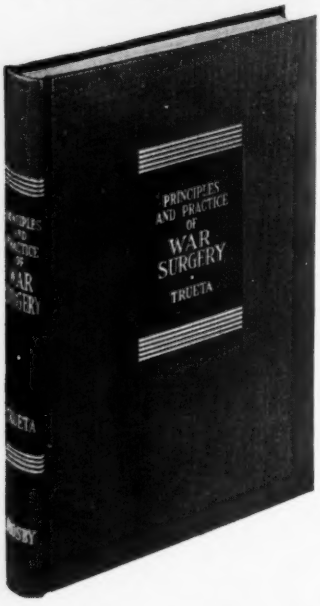

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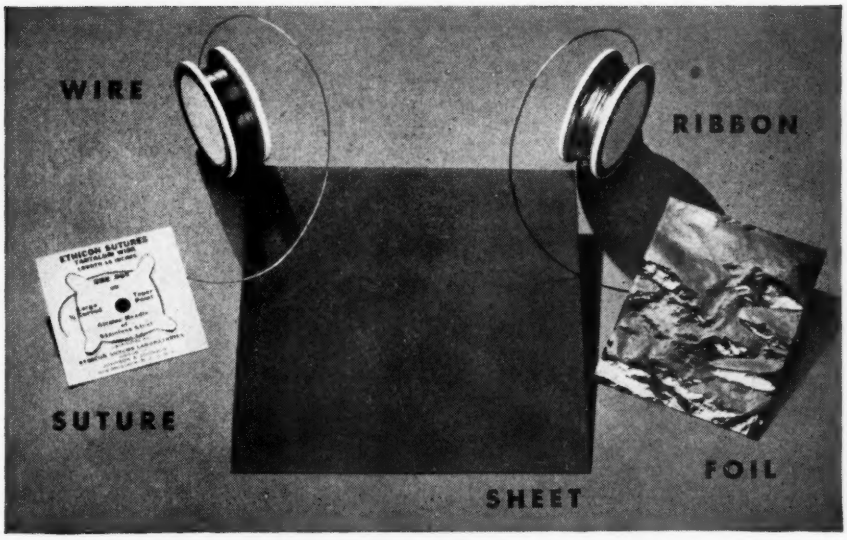

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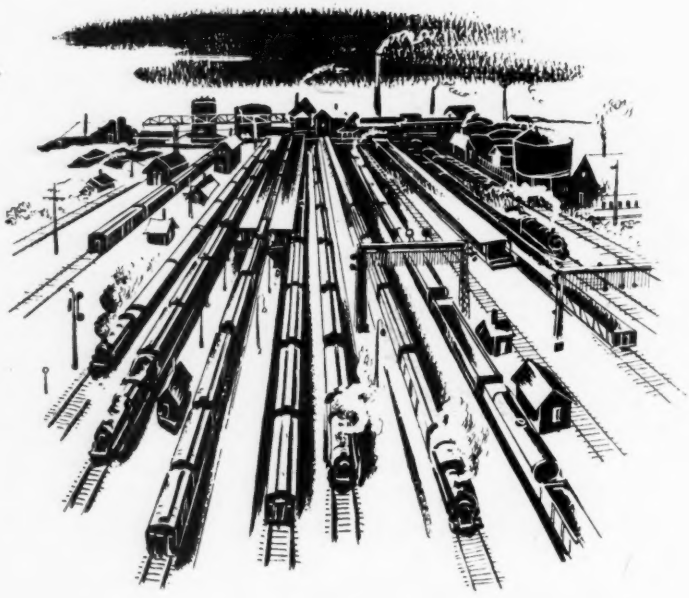

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Original Communications

Symposium on Surgical Lesions of the Thyroid

DIFFUSE AND ADENOMATOUS GOITER AND GOITER INDUCED BY VARIOUS AGENTS

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GOITER, like many other pathologic processes, has been thoroughly described by numerous writers. In view of the brevity of this paper, however, we deem it pertinent to draw on the literature in a more or less limited manner and to utilize for the most part our own experience in the presentation of the pathology of diffuse colloid goiter, diffuse hypertrophic parenchymatous or exophthalmic goiter, and hypertrophic parenchymatous or exophthalmic goiter with adenomas and adenomatous goiter with and without intra-adenomatous parenchymatous hypertrophy. The diffuse hypertrophic parenchymatous or exophthalmic goiter and hypertrophic parenchymatous or exophthalmic goiter with adenomas have been variously designated Parry's disease, Flajani's disease, Basedow's disease, and Graves' disease. In addition to the foregoing goiters, we shall call attention to certain other goiters that have been incidental findings in man and deliberately induced in experimental animals by various agents.

DIFFUSE COLLOID GOITER

The diffuse colloid goiter, which used to be observed frequently from prepuberty to late adolescence, according to Haines[1] is rarely observed today by the clinician. Furthermore, it is almost never seen by the surgical pathologist. This type of goiter, as its name implies, presents itself macroscopically on section as a vesicular, usually soft,

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sticky, glistening colloid mass (Fig. 1). On microscopic examination the goiter consists of follicles or vesicles of various sizes lined with cuboidal or flat epithelium and distended with a pale eosin-staining (acidophilic) thin colloid (Fig. 2).

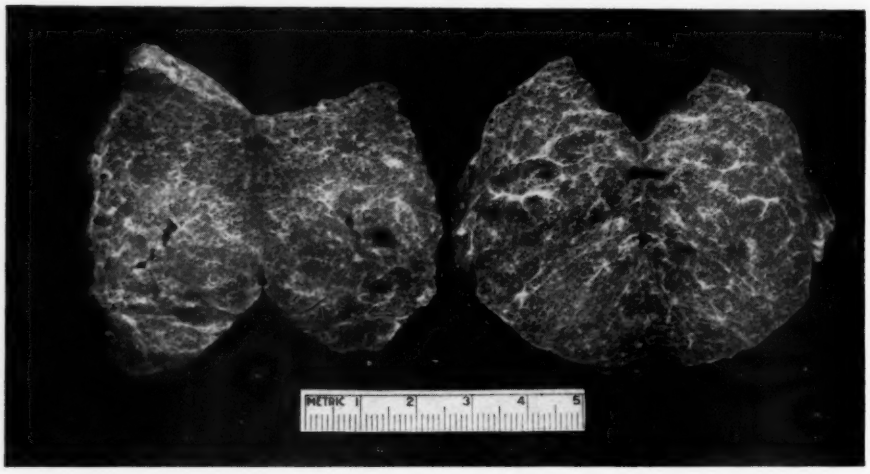

Fig. 1.—Diffuse colloid goiter showing vesicles filled with colloid.

Fig. 2.—Diffuse colloid goiter shown in Fig. 1; follicles are lined for the most part with flattened epithelium and contain thin pale-staining acidophilic colloid (hematoxylin and eosin ×75).

Hertzler[2] attached physiologic, clinical, and pathologic significance to the staining properties of colloid. He pointed out that normal colloid is acidophilic and stains pale pink with eosin, that if the stain is less intense than normal, the colloid is thin, and that pale-staining colloid is usually associated with cellular hyperplasia, is most marked in toxic goiters, and is to a degree a measure of toxicity. He further stated that thick colloid is indicated when the staining with eosin is more intense than normal, that it is commonly present in old goiters especially when there is degeneration of the connective tissue, and

Fig. 3.—Diffuse nonadenomatous exophthalmic goiter in which the normal contour of the thyroid is preserved (thyroid-shaped goiter of MacCarty).

that colloid which stains deeply with eosin is in the last stage of usefulness. The colloid that stains with hematoxylin, or basophilic colloid, he considered pathologic. He stated that basophilic colloid is associated with an atrophic and degenerated epithelium and that on the whole it is more pronounced in old goiters that are the seat of degenerative changes and in goiters associated with heart failure. These observations suggest the possibility that colloid of this type is representative of a substance which affects adversely the heart function and that those acini which contain basophilic colloid are permanently functionless.

DIFFUSE HYPERTROPHIC PARENCHYMATOUS THYROID OR EXOPHTHALMIC GOITER

Before H. S. Plummer[3] instituted the preoperative administration of compound solution of iodine to patients with exophthalmic goiter, the diffuse nonnodular and nonadenomatous hypertrophic parenchymatous goiter as seen by the surgical pathologist was a light brownish to reddish, fairly fine-grained, firm gland, regular in outline and often comparable in appearance to veal or beefsteak. Because its contour remains for the most part like that of the normal gland, MacCarty[4, 5] termed it a "thyroid-shaped goiter" (Fig. 3). Colloid, although present in all exophthalmic goiters prior to the universal preoperative

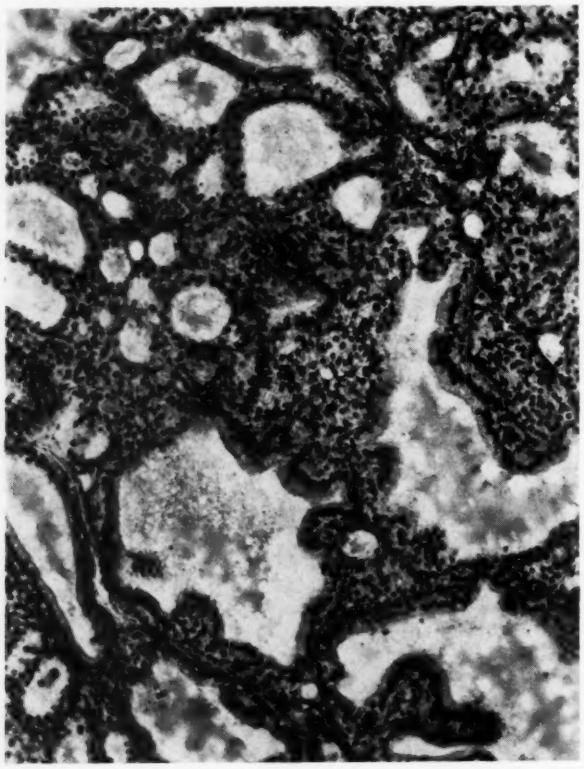

Fig. 4.—Diffuse nonadenomatous exophthalmic goiter showing follicles of various shapes and sizes lined with epithelium that ranges from cuboidal to high columnar and containing a small amount of thin pale-staining acidophilic colloid (hematoxylin and eosin ×125).

administration of compound solution of iodine, was not an outstanding feature at that time. The usual microscopic picture was that of round, oval, or irregular follicles lined with epithelium which ranged in form from cuboidal to high columnar. The follicles also were characterized to a large extent by a papillary infolding of the epithelium and contained a small to a moderate amount of colloid of varying density

(Fig. 4). It was rather unusual to see an exophthalmic goiter of which the colloid content was comparable to that of a colloid goiter.

Since the advent of administration of compound solution of iodine, the typical meaty exophthalmic goiter is seen much less frequently and has for the most part been replaced by a gland comparable to a colloid goiter, although smaller. The change in the exophthalmic goiter is undoubtedly attributable to administration of the compound solution of iodine. Following administration of compound solution of iodine, the epithelium changes from columnar to a low cuboidal or flat type and the acini dilate or at least have larger lumina, and their colloidal content increases (Fig. 5). This increase in the size of the

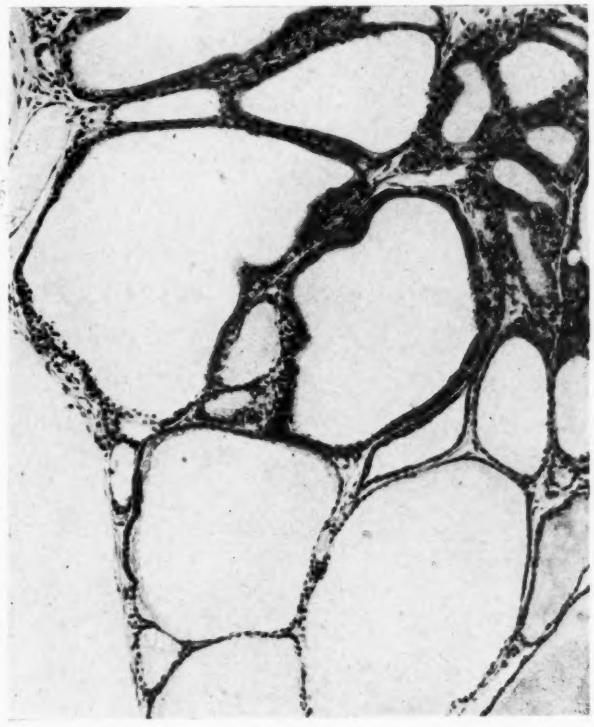

Fig. 5.—Diffuse nonadenomatous exophthalmic goiter showing the effect of the administration of compound solution of iodine. The cells lining the follicles are for the most part flat or low cuboidal with some low columnar epithelium still present. The colloid dropped out in preparation of the section (hematoxylin and eosin ×100).

lumina is probably the result of the diminution in the size of the cells. Some exophthalmic goiters on the other hand are more or less resistant to the changes that usually take place after administration of compound solution of iodine.

HYPERTROPHIC PARENCHYMATOUS THYROID OR EXOPHTHALMIC GOITER WITH ADENOMAS

The adenomas (Fig. 6) in hypertrophic parenchymatous thyroid or exophthalmic goiter may have follicles lined with columnar epithelium

like those seen in the extra-adenomatous portions of the goiter and, in addition, other follicles lined with cuboidal or flattened epithelium and more or less filled with colloid. Fetal acini or small undeveloped follicles lined with cuboidal epithelium and containing little or no colloid also may be present. The nodules sometimes observed in hypertrophic parenchymatous thyroid or exophthalmic goiters with or without adenomas differ from the true adenomas of exophthalmic goiter in that

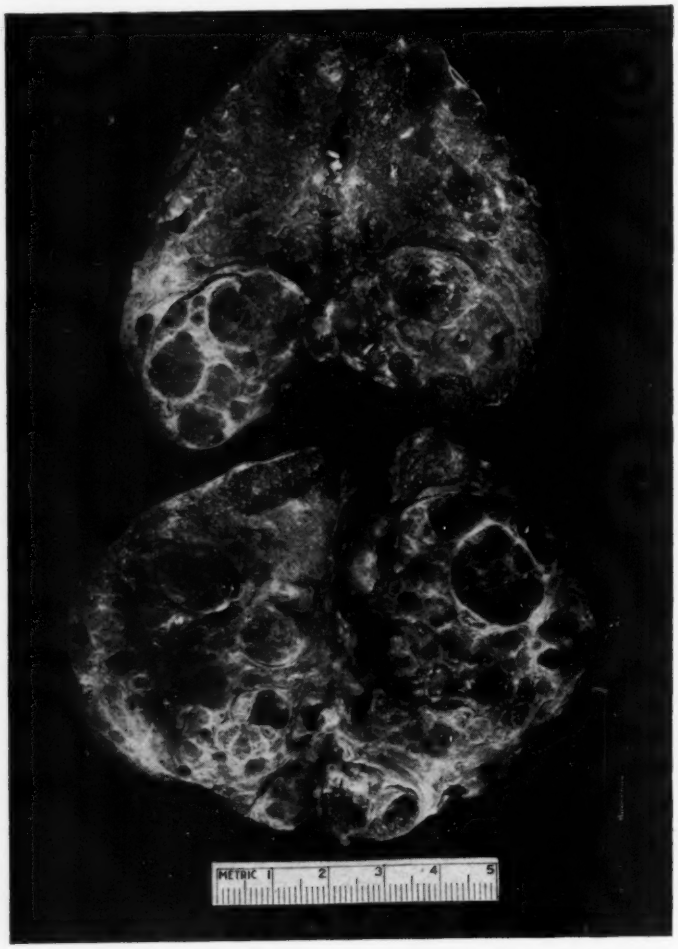

Fig. 6.—Multiple adenomas in a hypertrophic parenchymatous thyroid or exophthalmic goiter.

they are not encapsulated, rarely contain true fetal acini, and under the microscope usually resemble the extranodular part of the goiter. In other words the nodules are to a large extent comparable to the nodules observed in hyperplasia of the prostate gland.

In all hypertrophic parenchymatous thyroids or exophthalmic goiters, that is, in the diffuse nonnodular, the nodular, and the adenomatous types, varying degrees of chronic thyroiditis may be present. The

chronic thyroiditis in these goiters is characterized by fibrosis and lymphocytic infiltration of the interfollicular tissue, with or without formation of germ centers. This inflammatory reaction is probably attributable not to bacterial activity but to toxic products of the goiter. To some extent this form of thyroiditis may be activated by compound solution of iodine, as it has been more in evidence since the therapeutic use of compound solution of iodine began.

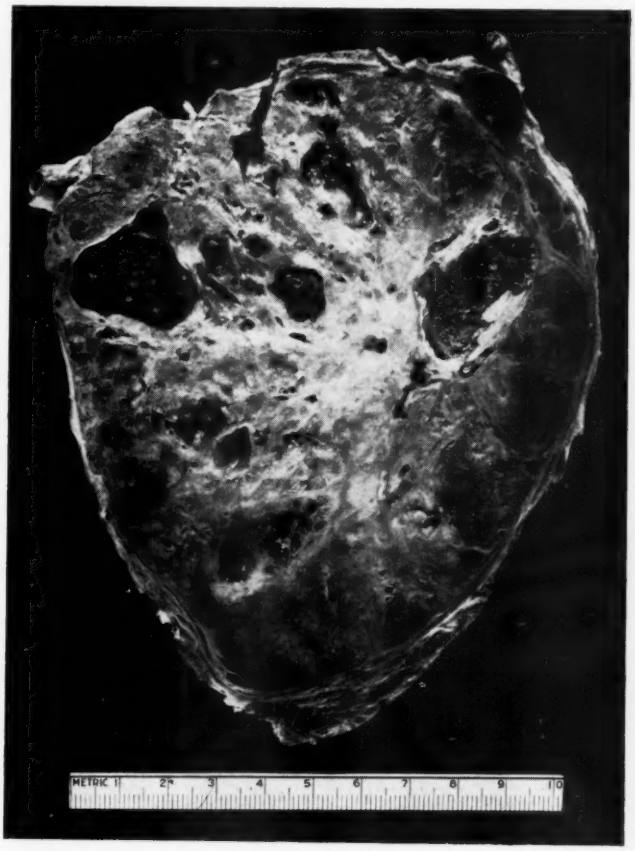

Fig. 7.—Partially degenerated, well-encapsulated adenoma of the thyroid.

Warthin[6] was of the opinion that the most important histologic criterion of Basedow's disease, toxic adenoma, and so forth is the presence throughout the thyroid gland of hyperplastic primitive lymph nodes with germinal centers giving evidence of lymphoid exhaustion. Warthin observed that in exophthalmic goiter, toxic adenoma, and so forth the pathologic picture of hyperplasia of the primitive lymph nodes of the thyroid, hyperplasia of the thymus, and other anatomic stigmas of the thymicolymphatic constitution is present. He was of the opinion that Basedow's disease, toxic adenoma, and so forth are pathologic reactions potentially predetermined at birth by virtue of a constitutional anomaly. This constitutional anomaly he preferred to

call "Graves' constitution." He went further and stated that the presence throughout the thyroid gland of hyperplastic primitive lymph nodes with germinal centers which give evidence of lymphoid exhaustion determines the existence of the Graves' constitution and that

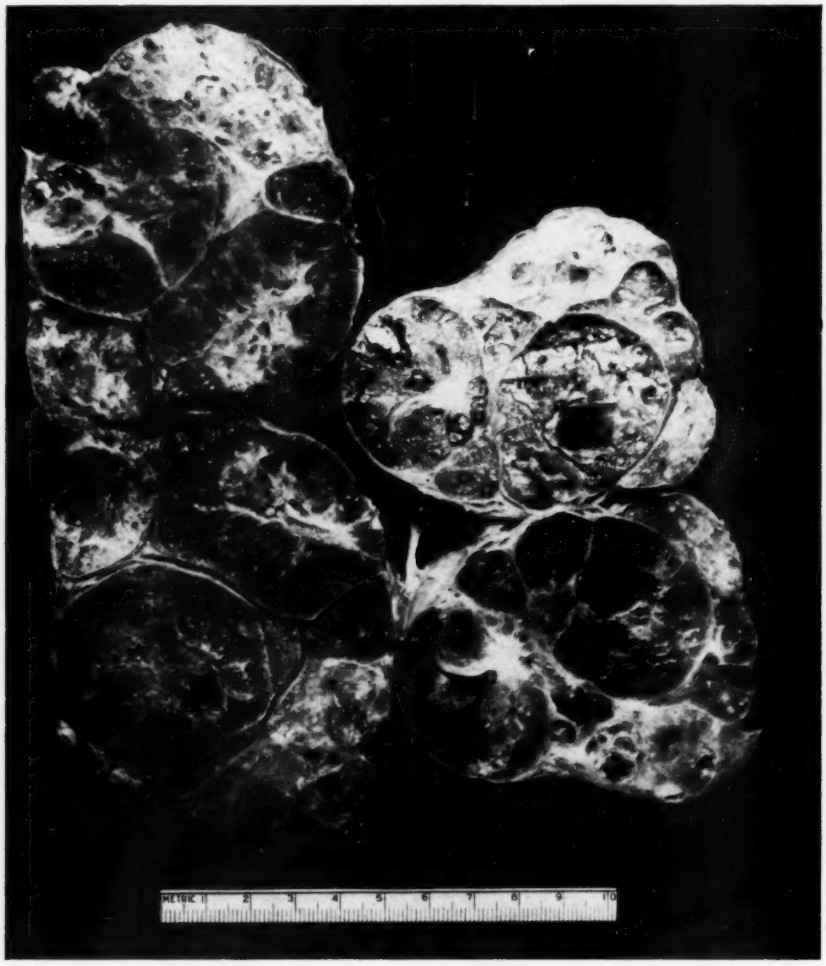

Fig. 8.—Multiple, variously sized, well-encapsulated adenomas of the thyroid.

evidence of this constitution may be recognized in the thyroid glands of young children. He considered Graves' constitution to be the underlying pathologic and clinical entity of exophthalmic goiter, toxic goiter, and toxic adenoma.

ADENOMATOUS GOITER

Adenomas may occur singly (Fig. 7) but usually they are multiple (Fig. 8). They vary markedly in size, from soft to firm in consistency and from a light amber to a reddish brown in color; they are encapsulated. They may undergo various types of degeneration, such as

hemorrhagic, fibrous, hyaline, calcareous, lipoid (granular), and cystic. Macroscopically and microscopically, true adenomas differ from the surrounding thyroid tissue.

At this point we deem it pertinent to state that we agree with the following statement in the summary of Graham's[7] classical article. He said, "By analogy and by the principles of general pathology, the encapsulated masses of nonlobulated thyroid tissue that do not invade, do not metastasize, and do not present histological characteristics which may be recognized as those of cancer, should be classified among the adenomas until we are sufficiently well acquainted with neoplasms from an etiological and biological standpoint to do otherwise."

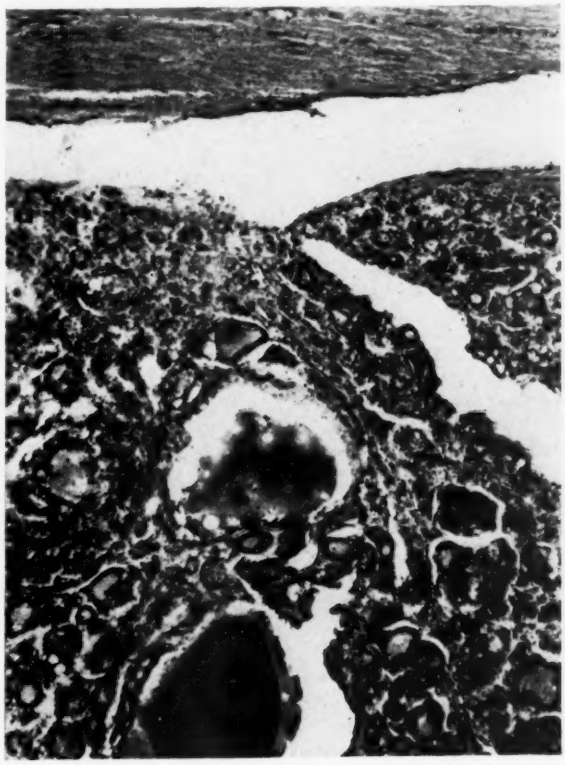

Fig. 9.—Adenoma of thyroid (Fig. 7) showing fetal follicles of various sizes and two large follicles containing fairly dense acidophilic colloid (hematoxylin and eosin ×75).

Microscopically, the arrangement, shape, and size of the epithelial cells vary in different adenomas and in different parts of the same adenoma. The cells may appear in diffuse masses without formation of acini (undifferentiated fetal adenoma), in small fetal acini with small lumina containing no colloid, in large fetal acini with larger lumina and with a small content of colloid or in well-developed acini lined by cuboidal or columnar cells, and with large lumina filled with

colloid. These adenomas usually contain fetal acini or follicles in addition to well-developed acini which contain colloid (Fig. 9). Columnar epithelium, not infrequently presenting a papillary, infolding effect, appears most often in adenomas associated with the hypertrophic, parenchymatous thyroid gland of exophthalmic goiter, less often in toxic adenoma, a clinical entity recognized and described by H. S. Plummer,[8-10] and rarely in nontoxic adenoma. The toxic adenoma cannot be distinguished macroscopically from the nontoxic adenoma, nor can it always be distinguished microscopically. However, when an adenoma of the thyroid gland is seen in which columnar epithelium is prominent, it is safe to consider it a toxic adenoma; the degree of

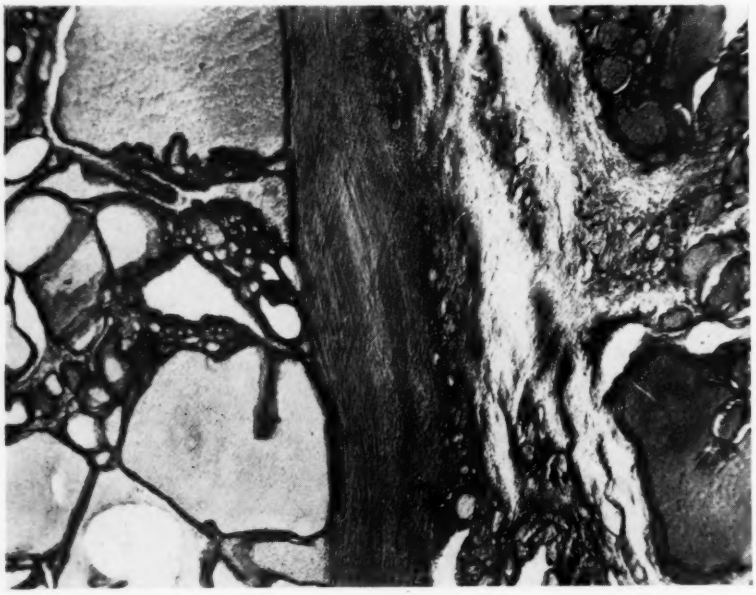

Fig. 10.—Toxic adenoma on left side showing follicles of various sizes part of which are lined with columnar epithelium with papillary infolding much in evidence. There is a well-defined capsule in the middle with practically normal thyroid gland on the right side (hematoxylin and eosin ×40).

toxicity probably depends on the amount of columnar epithelium and on the size and number of such adenomas in the gland. Johnson[11] found intra-adenomatous hypertrophy in 37.4 per cent of cases in which a diagnosis of adenomatous goiter with hyperthyroidism was made, whereas in cases in which the diagnosis was adenomatous goiter without hyperthyroidism he found intra-adenomatous hypertrophy in only 19 per cent. In order to make a microscopic diagnosis of toxic adenoma, the columnar epithelium, which may occasionally be associated with a papillary infolding, must be limited to the adenoma. In other words, the extra-adenomatous thyroid tissue should be practically normal, or at least should not show the microscopic features of exophthalmic goiter (Fig. 10).

GOITERS INDUCED BY VARIOUS AGENTS

In recent years certain interesting and important forms of goiter have been observed after the administration of a variety of agents. Some of these goiters are now coming to the attention of the pathologist.

One of the first of these forms of goiter to be noted in man was that seen in patients receiving thiocyanates over a prolonged period in the treatment of hypertension. Occasional enlargement of the thyroid gland during the administration of thiocyanates was reported by Barker[12] in 1936, and by Barker, Lindberg, and Wald[13] in 1941. Kobacker[14] in 1942, Fahlund[15] in 1942, and Foulger with Rose[16] in 1943 each reported an instance of enlargement of the thyroid gland following thiocyanate therapy. Rawson, Hertz, and Means,[17, 18] in 1942 and 1943, published a thorough study of thiocyanate goiter in

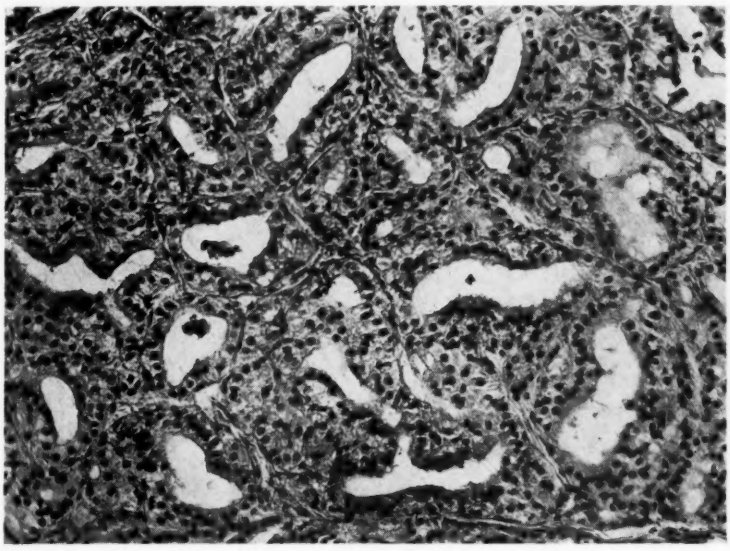

Fig. 11.—Thiocyanate goiter; the pathologic picture is comparable to that of an exophthalmic goiter (hematoxylin and eosin ×125). (Courtesy of Dr. Eugene B. Potter.)

man, with histologic and metabolic studies. Potter[19] in 1944 reported two cases of thiocyanate goiter and described the microscopic findings. In these cases the thyroid gland is enlarged but the metabolic rate is reduced. Exophthalmos is present in some cases. The thyroid gland on biopsy or resection shows parenchymatous hypertrophy (Fig. 11). The gland is cellular; the epithelium is cuboidal to columnar and the colloid generally is scanty or absent. The acini are small. Discontinuance of thiocyanate therapy or administration of desiccated thyroid results in return of the gland to normal size and an elevation of the metabolic rate.

Astwood,[20] and Hertz and Roberts[21] produced similar results in rats, that is, enlargement and hyperplasia of the thyroid gland and lower-

ing of the metabolic rate by the administration of sodium or potassium thiocyanate. Simultaneous administration of potassium iodide inhibited this effect.[20]

Goiter produced by thiocyanates in many respects resembles a form of experimental goiter of great interest since it was first reported by Chesney, Clawson, and Webster[22] in 1928, the so-called "cabbage goiter" or "cyanide goiter." Marked enlargement and hyperplasia of the thyroid gland and a lowering of metabolism developed in rabbits fed on a diet consisting mainly of cabbage. A search for the active agent in cabbage and other Brassica plants demonstrated that cyanides, particularly methyl cyanide, were effective in producing a similar goiter when administered to rabbits.[23] Kennedy and Purves[24] found that they could produce goiter in rats by feeding seeds of the Brassica family (rapeseed).

The cabbage goiters and the cyanide goiters, like those produced by thiocyanate, can be prevented by the simultaneous administration of iodine. The administration of iodine after the development of goiter in rabbits, however, resulted in the onset of symptoms of severe, sometimes fatal, hyperthyroidism.[25]

Other important compounds recently found to have powerful goiter-producing effects fall mainly in two groups: (1) thiourea and various thiourea derivatives and (2) sulfonamides and related substances.

Kennedy[26] in 1942, reasoning that the goiter-producing effect of rapeseed might be due to a derivative of urea, injected allylthiourea into rats and found that it produced large goiters. Richter and Clisby[27] in 1941 produced marked hyperplasia of the thyroid of rats by administration of phenylthiocarbamide. MacKenzie, MacKenzie, and McCollum[28] in 1941 found that the administration of sulfaguanidine to rats resulted in enlargement of the thyroid, and in 1942 MacKenzie and MacKenzie[29] produced goiters by administering thiourea, diethylthiourea and allylthiourea as well as sulfaguanidine and other sulfonamide compounds. Astwood, Sullivan, Bissell, and Tyslowitz[30] in 1943 produced enlarged thyroid glands in rats with both sulfonamide compounds and thiourea.

The thyroid glands in the animals treated with thiourea and thiourea compounds are diffusely enlarged and reddened, and the vessels are enlarged. Microscopically the height of the acinar cells and loss of colloid from the follicles are increased greatly in this type of goiter. The follicles are increased in size and appear to be increased in number. The lumina are decreased in size, due in part to many papillary projections; some follicles are solid round or oval masses of cells.[30]

Astwood[20] in 1943 tested various compounds and found that 39 out of 106 substances used were effective in causing enlargement and hyperplasia of the thyroid gland in rats. He found that thiouracil, a derivative of thiourea, was the most effective substance in the thiourea group. Of the sulfonamide drugs and other derivatives of aniline,

sulfadiazine had the most active effect on the thyroid gland. Feldman, Hinshaw, and Mann[31] in 1944 in administering to guinea pigs a sulfone derivative, promizole, found that the thyroid glands became enlarged and hyperplastic. Higgins and Larson[32] in 1944 confirmed this result in rats.

It is of interest that the experimental production of goiter by cyanides and thiocyanates has been prevented by the simultaneous administration of iodine, whereas the goitrogenic effect of thiourea and sulfanilamide and related compounds cannot be prevented by administration of iodine, but can be prevented by the administration of desiccated thyroid or thyroxin. Administration of desiccated thyroid or thyroxin was also effective in reducing goiters after they had developed regardless of whether they had followed administration of cyanides, thiocyanates, thiourea, or sulfonamide compounds.

It has been assumed that the action of the various drugs which produce goiter is by means of an inhibition of, or interference with, the manufacture of the normal thyroid hormone.[18, 33] The resulting increase in activity of the thyroid-stimulating pituitary hormone brings about hyperplasia of the thyroid cells but does not bring about an increase in thyroid hormone, which is in fact reduced to subnormal levels. This inhibitory effect has been made use of clinically by the administration of thiourea or thiouracil to patients suffering from hyperthyroidism in the form of Graves' disease.[34-36] In addition to disappearance of toxic symptoms and a decrease in the basal metabolic rate, temporary increase in the size of the thyroid gland was observed in three of nine patients treated with thiouracil by Williams and Bissell.[36] Microscopically the thyroid gland in cases of Graves' disease treated with thiouracil shows extreme hyperplasia with heightened epithelium, marked papillary infolding, and mitosis in the epithelial cells.

We should like to take this opportunity to record our impression that in the thiocyanate goiter there is more cellular hypertrophy, it is therefore more nearly comparable microscopically to an exophthalmic goiter, and that the thiouracil goiter is more of a cellular hyperplasia with mitosis very much in evidence, and is therefore more comparable to a carcinoma of the thyroid.

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DIAGNOSIS OF THYROTOXICOSIS

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DEFINITION

THE term thyrotoxicosis applies to exophthalmic goiter, toxic adenoma, and mixed types of toxic goiter. Many investigators have come to the conclusion that the underlying pathology of exophthalmic goiter and toxic adenoma is the same and that any differences that are noted in the clinical picture are the result of variations in the response of the individual patient to the thyroid intoxication. This point of view is still not completely established. However, for the purpose of this article, all types of toxic goiter may be grouped together under the general term thyrotoxicosis.

SIGNS AND SYMPTOMS OF THYROTOXICOSIS

The most outstanding manifestations of thyrotoxicosis are:

Goiter
Nervousness and irritability
Tremor
Tachycardia
Palpitation

Other signs and symptoms of the disease are:

Exophthalmos
Loss of weight in spite of a good appetite
Increase in basal metabolism
Dyspnea and, in a few patients, cardiac decompensation
Increased perspiration, flushing of the skin, and dermographia
Systolic thrill and bruit over the thyroid
Emotional instability
Muscle weakness
Ease of fatigue
Fever
Nausea and vomiting
Diarrhea
Pressure symptoms from the goiter
Scantiness of menstruation and, in a few patients, rather long periods of amenorrhea
Increased excretion of calcium and decalcification of bone

Goiter.—Some differences between the syndrome known as exophthalmic goiter and that known as toxic adenoma should be pointed out.

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In general, the onset of the disease is much more abrupt in patients with exophthalmic goiter. Plummer estimated that in the patients seen at the Mayo Clinic, fourteen and one-half years elapsed, on the average, from the time of appearance of a nodular goiter until the onset of hyperthyroidism. The term exophthalmic goiter is a misnomer because the disease may be present without exophthalmos and without a goiter, although it is most unusual to observe the absence of both in the same patient. Even though the thyroid gland may not be enlarged, it is usually much firmer than normal and in patients who show very little enlargement, the increased firmness may be an important diagnostic sign, particularly if it is associated with the presence of a systolic bruit over one or both of the superior poles. A bruit and thrill do not occur in the normal gland. The problem of diagnosis is sometimes complicated by the fact that a large portion of the thyroid or even all of it may be in the substernal area. As a rule, only a portion of the gland lies substernally and when most of it is in the substernal space the upper edge can be palpated, particularly when the patient swallows. The presence of substernal nodules can often be detected by careful palpation during the act of swallowing. When thyroid tissue cannot be palpated, it can sometimes be demonstrated by roentgen-ray examination of the chest. The rare finding of the thyroid tissue below the level of the mediastinum, for example just above the diaphragm, may be borne in mind in some unusual cases in which thyrotoxicosis appears to be present but thyroid tissue cannot be located. It may be emphasized that it is unusual to be unable to palpate any thyroid tissue in patients with thyrotoxicosis, and goiters that are entirely confined to the substernal space so that no portion of them can be palpated are rare.

It is very important to use the correct method of palpating the thyroid. Best results are obtained by standing behind rather than in front of the patient. It is preferable to have the patient in the sitting position. The head may, if desired, be rotated slightly toward the side to be examined in order to relax the sternomastoid muscle. The trachea is displaced to one side by pressing against it with the fingers of one hand. The thyroid tissue on the opposite side of the neck may then be palpated by placing the thumb behind the sternomastoid and the fingers in front, taking care not to confuse muscle tissue with thyroid tissue. By manipulating both hands at the same time and having the patient swallow, it is possible to palpate almost all thyroid tissue that is present in the neck and also to feel the lower extremity of most goiters which have some substernal extension and to feel the upper end of most truly substernal goiters. Tissue on the opposite side of the neck is palpated by reversing the position of the hands and, if desired, rotating the head slightly toward that side. It is possible with careful palpation to outline all normal thyroid glands. Those that cannot be

palpated are usually very small and atrophic. Palpation is of great importance in doubtful cases. The detection of abnormal thyroid tissue, for example the presence of a few small nodules which extend substernally, may be the determining factor in deciding whether or not the patient has thyrotoxicosis.

In symmetrical enlargements of the gland with hyperthyroidism, a bruit which is systolic in time is frequently heard. It is usually most marked over the superior poles and may be audible all over the gland. It may or may not be accompanied by a systolic thrill. In nodular goiters with hyperthyroidism, a thrill and bruit are usually not heard.

Pressure symptoms from the goiter are noted in about one-third of the patients. They are usually not serious unless the goiter extends into the substernal space. Some distortion and compression of the trachea may occur. The pressure symptoms of toxic goiter must not be confused with the sensation of a lump in the throat which is so common in nervous women who do not have thyrotoxicosis.

Nervous Manifestations.—The nervousness of toxic goiter is fairly typical. It is characterized by restlessness, inability to sit still, irritability, and sudden fits of weeping without much justification. Many patients are easily frightened, worry a great deal, and are very sensitive before the onset of the disease. These tendencies are exaggerated after the development of toxic goiter. It is not always easy to be certain when nervousness and emotional instability are caused by thyrotoxicosis and when they are the result of some domestic difficulty or one of the other major problems of living. The nervous manifestations may be similar in both instances. In the case of toxic goiter, it is the combination of nervousness, irritability, and emotional instability with other manifestations of the disease which makes the diagnosis possible. A large percentage of patients referred to a thyroid clinic with the tentative diagnosis of thyrotoxicosis prove to have no overactivity of the thyroid at all and often are nervous women with domestic problems.

In general, the nervous manifestations of the disease are greater in patients with exophthalmic goiter than in those with toxic adenoma. Indeed, the presence or absence of emotional instability was considered by Plummer to be the most important sign in distinguishing between these two diseases.

Tremor.—The tremor of thyrotoxicosis is fine and rapid in contrast to the coarser, slower tremor of Parkinson's disease. There are, however, exceptions to every rule and in some instances the tremor is coarse. It should be pointed out that Parkinson's disease is sometimes accompanied by a syndrome resembling exophthalmic goiter. This phenomenon is of interest in view of the reported production of thyrotoxicosis in animals by injury to the base of the brain.

Cardiac Manifestations.—Palpitation and tachycardia are the rule. The most common finding is rapid, forceful beating of the heart. The

heart beats are often so forceful that they shake the whole chest wall. In a few instances the heart rate may be very little increased in spite of a great increase in the basal metabolism. In rare instances in which complete heart block is present, the onset of thyrotoxicosis may cause the heart rate to rise approximately to the normal level. A rough parallelism has been noted between the product of the pulse rate and pulse pressure and the level of the basal metabolism.

Dyspnea is common, particularly on effort. The increased work demanded of the heart is sometimes enough to produce cardiac decompensation, especially when the heart is independently damaged. Both transient and prolonged attacks of auricular fibrillation are not uncommon. Auricular flutter is rare. The onset of auricular fibrillation or cardiac decompensation or both usually means that the heart is independently damaged by arteriosclerosis or rheumatic fever. Attacks of true angina pectoris are not very common and when they do occur, tend to disappear after the disease has been abolished by suitable treatment. The presence of thyrotoxicosis must always be thought of in patients with unexplained auricular fibrillation and cardiac decompensation. The diagnosis is not always easy, particularly when toxic goiter occurs in apathetic individuals. The nervous manifestations of the disease may then be almost absent and what few there are can be elicited only by the most careful examination of the patient. Cardiac decompensation in itself may produce a considerable amount of increase in the basal metabolism.

The dyspnea of thyrotoxicosis is probably due in part to a specific chemical effect of the thyroid hormone on the heart muscle, as well as to overwork of the heart. The ease with which skeletal muscle fatigues in this disease is probably the result of a similar disturbance. Mechanical factors alone explain only part of the picture.

Neurocirculatory asthenia is sometimes confused with thyrotoxicosis because of nervousness, ease of fatigue, rapid forceful beating of the heart, and some increase in pulse pressure. Exophthalmos is not present. There is usually no goiter and the basal metabolism is normal.

Exophthalmos.—Exophthalmos of varying degree is noted in from 60 to 70 per cent of patients with exophthalmic goiter but is not commonly noted in persons with nodular goiters and hyperthyroidism. In determining the degree of exophthalmos, it is important to bear in mind the natural prominence of the patient's eyes before the onset of the disease. Puffiness of the eyelids is a very characteristic finding and is sometimes of more diagnostic value than exophthalmos. The prominence of the eyes may vary greatly in the same patient from time to time and varies greatly from patient to patient. One eye is often more prominent than the other. A great variety of eye signs have been described but only two of them are of much practical importance, namely, lid lag (von Gräfe) and poor convergence (Moebius). As the

exophthalmos increases, the movements of various extraocular muscles may be impaired, producing many abnormalities in the movements of the eyeball. When the condition is so marked that the eyelids cannot be closed, there is great danger of the development of a corneal ulcer. The condition may be so extreme that a prolapse of the eyeball occurs and it is occasionally necessary to resort to operative procedures in order to correct these malignant forms of exophthalmos. Exophthalmos may be the first sign of exophthalmic goiter and may precede the onset of an increase in basal metabolism by as much as six months. Bilateral exophthalmos means exophthalmic goiter until proved otherwise. When the condition is strictly unilateral it is necessary to consider the possibility of a tumor of the orbit pushing the eyeball forward.

Loss of Weight.—One of the most characteristic features of toxic goiter is loss of weight in spite of an increase in appetite. This phenomenon is the result of the increase in basal metabolism. Loss of weight is not invariable and weight may be gained if the ingestion of calories is sufficient to exceed the expenditure. The loss of weight may be rapid and extreme and, in general, the greater the loss of weight the more serious the condition of the patient. In gauging the risk of operation more attention is paid to the general nutritional state of the body than to any other factor. The most common conditions in which similar extreme loss of weight may be encountered are diabetes mellitus, pulmonary tuberculosis and other chronic infections, and carcinoma. The excretion of nitrogen in the urine of patients with toxic goiter may be very high, indicating rapid breakdown of tissue. For this reason, it is very important that the diet be high not only in calories but also in protein.

In diabetes mellitus weight is sometimes lost in spite of a good appetite. The presence of large amounts of sugar in the urine leaves little doubt about the diagnosis. However, toxic goiter and diabetes mellitus sometimes occur together. The diagnosis is then made by the finding of a high basal metabolism, goiter, nervousness, increased perspiration, and all the other manifestations of toxic goiter, together with the presence of large quantities of sugar in the urine and other manifestations of diabetes mellitus. While traces of sugar may be found in the urine of patients with toxic goiter without diabetes, the presence of large quantities almost invariably means that the patient has diabetes mellitus. When the glycosuria is mild and requires only small amounts of insulin for its control, it may disappear after a thyroidectomy.

Although pulmonary tuberculosis is commonly stated to be confused with toxic goiter, in our experience it rarely presents any problem. Pulmonary tuberculosis does result in loss of weight, tachycardia, and ease of fatigue, but is readily distinguished from toxic goiter by the poor appetite, normal basal metabolism (unless a fever is present),

absence of goiter, characteristic roentgen-ray findings, and the recovery of tubercle bacilli in the sputum and fasting gastric contents.

Gastrointestinal Symptoms.—Diarrhea occurs in less than one-third of the cases and usually in the more severe ones. An increase in appetite is the rule but in a few patients nausea and vomiting are noted. When present, they indicate that the disease is very severe and are strong presumptive evidence of an impending crisis. They are to be regarded in the most serious light and mean that treatment must be started at once. They sometimes persist in spite of the administration of iodine and under these circumstances indicate a bad prognosis.

Muscle Weakness.—Muscle weakness is almost always present to some extent and is easily demonstrated by difficulty in stepping up on a chair. The intensity of muscle weakness and emotional instability are directly related to the severity of the disease and the risk involved in operation. The development of muscle weakness is undoubtedly the result of a chemical disturbance in the muscle and is probably related to the metabolism of phosphocreatine. Muscle weakness diminishes as weight is gained during the administration of a high caloric diet which is high in protein.

Ease of Fatigue.—Ease of fatigue goes hand in hand with muscle weakness and bears a direct relationship to the severity of the disease. However, exceptions are noted and in some patients the disease produces at first an exhiliration and apparently increases the capacity for work.

Cutaneous Manifestations.—The skin is commonly warm, moist and flushed, although pallor may be present and there may be little increase in perspiration. The skin flushes easily just as it does in women with the menopausal syndrome and there is usually a dermographia.

Fever.—The temperature of the body is usually normal but in occasional instances a moderate elevation of the temperature appears to be explained only by the presence of thyrotoxicosis.

Menstrual Disturbances.—Scantiness of menstruation is common in toxic goiter just as profuse bleeding is common in hypothyroidism. The intermenstrual periods may be greatly prolonged. The longest period of amenorrhea which we have observed is nine months.

Effect on Calcium Metabolism.—Hyperthyroidism results in an increased excretion of calcium in the urine without any change in the concentration of calcium in the serum, in contrast to hyperparathyroidism which causes an increase both in the excretion of calcium in the urine and in the concentration of calcium in the serum. When hyperthyroidism is present for a long period of time, extensive decalcification of bone may result if the intake of calcium is low. Spontaneous fractures have been reported in rare instances as a result of this change. A minister is reported suddenly to have grown two or three inches shorter one Sunday while preaching, a few weeks after a thyroidectomy. He had suffered from spontaneous fractures of two vertebrae. On

roentgenologic examination the only change noted in hyperthyroidism is uniform decalcification. The bone cysts characteristic of hyperparathyroidism are not observed.

Increase in Basal Metabolism.—The most important laboratory guide to fluctuations in thyroid function is the determination of the basal metabolism. However, it is not to be relied upon too greatly and is not a substitute for a careful history and physical examination. It is, however, a very important aid in diagnosis and in following the effect of treatment. Too much emphasis cannot be placed upon the value of determining the level of basal metabolism instead of relying upon a single test. Before carrying out any treatment, the metabolism should be determined on successive days until a level is reached. Only in this way is it possible to determine the severity of the disease as judged by the amount of increase in basal metabolism and also to measure the effect of treatment, in particular that of iodine. In hospital patients the first metabolism is, on the average, about fifteen points higher than the level which is subsequently established. If a single determination is relied upon, false conclusions may be drawn. If the elevation is only moderate, the metabolism may drop to normal when it is repeated. False diagnoses of thyrotoxicosis may thereby be avoided. The amount of elevation of the basal metabolism bears a rough relationship to the severity of the disease, although many exceptions are noted. In general, the rate must be consistently elevated 15 per cent or more above the normal before it can be concluded that thyrotoxicosis is present. In doubtful cases, the influence of iodine or thiouracil on the rate of metabolism may be of diagnostic value. If the metabolism is reduced and the symptoms are alleviated during the administration of iodine or thiouracil, and the two increase when the administration of these drugs is discontinued, it may be assumed that thyrotoxicosis is present. The response to iodine is of special value when the increase in metabolism is slight and yet the symptoms of the disease appear to be definite. Under these circumstances, the administration of iodine may reduce the metabolism to a normal or even to a subnormal level. In rare instances, particularly following a subtotal thyroidectomy, patients appear to be thyrotoxic in spite of the presence of a normal level of metabolism. In such patients the rate may drop to between minus 15 and minus 25 per cent in association with clinical improvement. Nervousness will reappear when iodine is omitted and the metabolism rises to normal. In such patients the subnormal level of metabolism produced by iodine may possibly represent their true normal level, so that a standard normal level would be, for them, a thyrotoxic one. In other patients with a normal level of metabolism following operation, the administration of iodine may produce myxedema with a lowering of the metabolism. These abnormalities disappear when the administration of iodine is discontinued.

Observation of the influence of thiouracil on the basal metabolism may now be substituted for that of iodine in many patients as a diagnostic procedure. The chief objection to thiouracil for this purpose is that a much longer period of time is required for the maximum effect on the metabolism to appear (from thirty to thirty-five days, compared with from seven to ten days for iodine).

OTHER DISEASES IN WHICH THE BASAL METABOLISM IS ELEVATED

Thyrotoxicosis is not the only cause of an increase in basal metabolism. It may be elevated in the following conditions:

1. Acromegaly
2. Lymphatic and myelogenous leucemia.
3. Essential hypertension
4. Overdose of desiccated thyroid or thyroxine
5. Administration of various drugs such as dinitrophenol, dinitro-ortho-cresol, diiodothyronine, adrenalin, caffeine, atropine, camphor
6. Exercise
7. Ingestion of food
8. Fever
9. Pregnancy
10. Cardiac decompensation
11. Polycythemia vera
12. Pernicious anemia

Acromegaly.—In some patients with acromegaly a syndrome resembling exophthalmic goiter may be present with moderate exophthalmos, goiter, palpitation, tremor, increased perspiration, and a high basal metabolic rate. These symptoms are the result of overproduction of the thyrotropic factor by the anterior lobe of the pituitary. Indeed, overproduction of this factor may be an important cause of thyrotoxicosis. When acromegaly is well developed, the diagnosis is easy. In the early stages of the disease before the skeletal changes have become clear-cut, it may be difficult to determine whether acromegaly is present or not. Accurate diagnosis is important because when thyrotoxicosis is associated with acromegaly, it is treated by attacking the pituitary and not the thyroid. It should be emphasized that in the thyrotoxicosis accompanying acromegaly, a reduction in basal metabolism is noted during the administration of iodine, just as it is in thyrotoxicosis without acromegaly.

The Leucemias.—Increases in basal metabolism of as much as 70 per cent may be noted in patients with lymphatic and myelogenous leucemia. The increase appears to be somewhat proportional to the increase in the white cell count and is reported to drop when the disease improves with roentgen-ray therapy. The clinical pictures in the leucemias are so different from those presented by thyrotoxicosis that they

rarely give rise to problems in diagnosis, although exophthalmos, high pulse rate, and increased sweating may be present. There are reports of confusion in the literature.

Essential Hypertension.—In a fairly large percentage of patients with essential hypertension there is an increase in basal metabolism of as much as 30 per cent. Its cause is obscure. When associated with a goiter, it sometimes results in an incorrect diagnosis of thyrotoxicosis and leads to a thyroidectomy. It does not disappear, however, following this operation. Observation of the influence of iodine and thiouracil on the basal metabolism in these patients is of great diagnostic value.

Overdose of Desiccated Thyroid or of Thyroxine.—In a few obese patients a syndrome resembling thyrotoxicosis is observed following the ingestion of excessive amounts of desiccated thyroid or of thyroxine for purposes of weight reduction. Elevations in basal metabolism of as much as 50 per cent are sometimes observed. If the patient happens to have a goiter, the presence of loss of weight, tremor, increased perspiration, and palpitation may make the diagnosis difficult. In doubtful cases it is always wise to inquire about the ingestion of thyroid products. Symptoms disappear promptly following the omission of the drug.

Administration of Various Drugs.—Increases in basal metabolism from the administration of various drugs do not present very much of a diagnostic problem. Great increases in metabolism may be produced by dinitrophenol and dinitro-ortho-cresol, which appear and disappear much more quickly following the administration and omission of these drugs than after the administration and omission of the thyroid hormone. The clinical picture produced by these two drugs is quite different from that produced by thyrotoxicosis. For example, patients with myxedema remain myxedematous when the basal metabolism is raised from minus 40 per cent to normal by their administration. Diiodothyronine (thyroxine minus 2 atoms of iodine) produces an increase in basal metabolism which also appears and disappears more quickly following the administration of the drug, than does that produced by the thyroid hormone. This material is used only experimentally and therefore does not present a problem in diagnosis. Adrenalin produces a moderate increase in basal metabolism which reaches its maximum in fifteen minutes and disappears in sixty minutes after administration of a single dose. Following a single dose of 10 mg. of thyroxine intravenously to an individual with a normal level of metabolism, the maximum increase appears within two to three days and disappears within twenty days. In patients with myxedema, the maximum appears within three to ten days and disappears within seventy to ninety days. Overproduction of adrenalin may present a diagnostic problem in rare instances in which there is a tumor of the adrenal medulla. Other manifestations of the disease are different from those of thyrotoxicosis and tend to occur in paroxysms. Caffeine is reported

to cause an increase in basal metabolism of from 7 to 23 per cent in a dose of from 0.5 to 0.7 Gm. and atropine and camphor are reported to produce somewhat smaller increases. The minor effects of these drugs merely emphasize the necessity of carrying out basal metabolism determinations under basal conditions.

Exercise.—There is a direct relationship between heat production in muscular exercise and the amount of energy expended in the muscular activity. There is a direct parallelism between the minute volume of the heart and the increase in basal metabolism.

Ingestion of Food.—Slight increases in basal metabolism have been observed following the ingestion of various foodstuffs, particularly protein, which exerts a specific dynamic action greater than that of carbohydrate or fat. Following the ingestion of very large quantities of protein and basal metabolism may rise as much as 20 per cent.

Fever.—An increase in basal metabolism has been noted in patients with fever, which amounts approximately to 7 points for each degree Fahrenheit that the temperature is raised and 10 points for each degree centigrade.

Pregnancy.—Increases in basal metabolism of as much as 25 per cent may be noted in the last three months of pregnancy. The increase has been commonly considered to be proportional to the combined surface area of the mother and child, although some of the increases are greater than could be accounted for in this manner. In rare instances, increases of as much as 40 per cent have been noted and seem to be explained only by some hormonal change involving increased production of thyroxine, which in turn may be secondary to some pituitary disturbance. In patients with goiters, either before or after thyroidectomy, it is not always easy to be certain when an increase in basal metabolism is entirely the result of the pregnancy and when it is the result of some overactivity of the thyroid. A diagnostic trial of iodine administration may be helpful.

Cardiac Decompensation.—In patients with cardiac decompensation the basal metabolism may rise as much as 50 per cent above normal. This increase rarely presents a diagnostic problem because it is unusual to carry out basal metabolism determinations in patients with cardiac decompensation.

Polycythemia Vera and Pernicious Anemia.—In polycythemia vera and pernicious anemia slight increases in basal metabolism have been reported but these diseases do not present diagnostic problems.

THE HEART AND CIRCULATION IN PATIENTS WITH HYPERTHYROIDISM

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THE problems encountered in the treatment of the heart in patients with hyperthyroidism can best be understood by a study of the effects of hyperthyroidism on the physiologic behavior of the normal circulation. It is clear that if the patient has already acquired heart disease prior to the hyperthyroidism the pathologic changes will be influenced by both processes. In general the changes in the physiology of the circulation can be attributed largely to overwork and undernutrition. This discussion will be guided by this concept.

RESPONSE OF THE CIRCULATION TO THE PRODUCTION OF EXTRA HEAT

Peripheral Blood Flow.—The patient with hyperthyroidism has an increased energy expenditure and a corresponding heat production. The heat is liberated within the body, largely in the muscles, and is transported to the surface by the blood. The surface is a complex structure composed of three units which are functionally integrated to regulate the loss of heat. The outer or papillary layer has immediately beneath it, capillaries through which the blood flows from the arterioles, and it is exposed to the temperature of the surrounding environment. Beneath this is a subpapillary layer of capillary and venous plexuses. According to Wollheim[1] this layer acts as a reservoir in which the blood becomes trapped and through which the blood moves from five to twenty-five times slower than in the adjacent end capillaries of the skin papillae. Attention has been drawn previously to this depot function of the skin by Meek and Eyster.[2] The blood thus withdrawn from the circulation may at times amount to 1,800 c.c. Finally there is the subcutaneous layer, which contains variable amounts of fat and a plexus of larger vessels. The quantity of fat and fluid present in this layer modifies its character and changes its capacity for the transfer of heat.[3]

As the blood circulates through this surface layer its temperature is reduced and approximates that of the surface of the skin. The rectal temperature measures the temperature of the blood at the sites of heat formation and at its entrance to the surface. The difference between the skin and rectal temperatures gives the gradient of heat flow. If the rectal temperature does not change, then all the heat produced is being eliminated. Knowing the amount of heat produced in a unit's time (basal metabolic rate), the specific heat of the blood,

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and the difference between the skin and rectal temperatures, the quanity of blood required to deliver this amount of heat to the surface can be computed. This quantity of blood represents the peripheral blood flow. If the peripheral layer is exposed to a cool environment, loss of heat by radiation occurs readily, the skin temperature is decreased, the gradient of heat flow is increased, and a smaller blood flow will be required. If the environment is warm but relatively dry, then the insensible perspiration is easily vaporized, the surface is cooled, the gradient is maintained, and the blood flow is reduced. Under hot moist environments (tropical conditions), the surface cannot be cooled, the gradient will be reduced, and the blood flow will be increased to a maximum. Unless the heat produced in a unit's time can be transported to the surface and eliminated in the same unit of time, it will be stored in the body and its storage will be reflected in the rise of the rectal temperature. Increase in rectal temperature is associated with an increase in heat production of 7 per cent for every degree rise (F.) in temperature. Thus storage of heat leads to the development of a vicious cycle. Keeton and co-workers[4] using this method have reported that normal subjects exposed to hot moist environments may increase their peripheral blood flow as much as seven times as compared to the blood flow under comfortable conditions. Under such an increased blood flow there was no storage of heat and no increase in heat production. Stewart and Evans[5] using similar methods have studied the peripheral blood flow in patients with hyperthyroidism who were exposed to an average environmental temperature. They found that the peripheral blood flow bears a linear relationship to the basal metabolic rate, and concluded that this increase in blood flow was correlated with heat disposal. The clinical signs of maximal vasodilatation seen in hyperthyroid states are familiar to all. They consist of the warm, moist, flushed skin, capillary pulsation, and low diastolic blood pressure.

Increase in Blood Volume.—If the blood flow through the periphery is increased from three to seven times it is obvious that the extra blood must be obtained by either shunting it from the interior (viscera, lungs, muscles) to the surface or by increasing the circulating volume. Keeton and associates[6] have shown in conditions where there is an embarrassment in heat elimination unassociated with an increase in heat production the circulating blood volume is not regularly increased. The blood is obtained by shunting it from the interior. The extra blood is obtained from the reserve depots, the subpapillary layer of skin, spleen, liver, and lungs. The conversion of a slowly moving stream of blood normally present in the subpapillary layer to a rapidly moving one, and the establishment of a free access of the circulating blood volume to this peripheral layer serves the double purpose of giving a larger volume of blood for the convection of the heat and a more advantageous disposition of the blood for heat loss.

In hyperthyroidism with its extra heat production, the peripheral blood flow is maintained not only by shunting blood from the interior but also by an actual increase in blood volume.[7]

Acceleration of Blood Flow.—In the normal subject at work, extra heat is produced. The heart responds by increasing its rate and its output per minute. This adjustment may be explained, in part, as secondary to the increased filling of the heart and the increased circulating volume. In hyperthyroidism the increase in cardiac output is greater at the same oxygen consumption than it is in work. This suggests that the heart in hyperthyroidism is hyper-reactive and that there are other factors than the demand for the transport of extra heat operative. This view is supported by the report of various investigators[8] who found that if a rabbit is rendered hyperthyroid by thyroid feeding and the heart is then removed, the isolated organ continues to beat at a rate much faster than the heart of a normal control. This view is further supported by the clinical observation that in patients with good compensation tachycardias exist which are out of proportion to the increases in their basal metabolic rates. This acceleration of the circulation can be approximately measured by determining the circulation time (arm to tongue). Clinically this activity of the circulation is revealed by a diffuse precordial pulsation, widespread pulsations of the arteries, loud abrupt apical heart tones, and increased pulse pressure.

BEHAVIOR OF THE CIRCULATION IN VASOMOTOR INSTABILITY WITH NORMAL HEAT PRODUCTION

The circulatory adjustments of patients with vasomotor instability must be understood if errors in diagnosis are to be avoided. These patients present bizarre clinical pictures, and are classified variously by the examining physicians. One man will say that the patient is suffering from somatic fixation, another will find that he has a cardiac neurosis or anxiety state, but all will wonder whether the patient may not have hyperthyroidism. It is quite helpful to think of these individuals as suffering from vasomotor instability and to assume that there may be many causes for this instability. The differential diagnosis hinges on the fact that although they may appear to be producing extra heat, in reality they have a normal heat production. If one looks for signs of increased peripheral blood flow, they will be lacking. The skin may be flushed over the face and neck, but it will not be rosy elsewhere. If the hand is held over the skin a sensation of warmth will not be felt as in hyperthyroid patients. The skin may be moist in places but it feels cold. Goldbloom[9] has shown that in these patients neither the blood volume nor the cardiac output is increased. The physiologic difficulty lies in the adjustment of heart action to the changing vascular bed produced by reflex stimulation of various types. The patients often have an irritable cartoid sinus.

Pressure over the sinus may not only slow the heart significantly but it may also inhibit inspiration. It is quite certain that there is a similar irritability of the reflexes originating from the arch of the aorta. These patients may have episodes of tachycardia precipitated by a change in their position from the horizontal to the vertical. They appear at times to be suffering from orthostatic hypotension. If one takes a circulation time during an episode of tachycardia it will be shortened. If, however, this is repeated under basal conditions at the same time as the metabolic rate a normal circulation time will be observed.

One may also be misled by the increase in the metabolic rate (25 to 35 per cent) when taken by the oxygen consumption method. If the respirations of these subjects are observed, they will be found to be irregular, at times quite shallow, and at other times unusually deep and sighing in character. This can be seen best on examination of the spirometer tracings taken while the subject is breathing oxygen. In the protocals of Goldbloom[9] it was noted that the respiratory quotients tended to be high. This would indicate that at times hyperventilation was occurring. The patients often have a subcyanotic color to the finger tips. Hick and associates[10] have found in some cases a definitely low oxygen saturation of the arterial blood. One can, therefore, understand that if a patient has a low oxygen saturation of hemoglobin, he would show an increased oxygen utilization when allowed to breathe oxygen. In this manner a false positive increased metabolic rate would be obtained.

The definitive diagnosis can usually be made by searching the patient's history for evidence of extra heat production, by studying the quantity of food eaten, the changes in his weight, and above all by looking for psychoneurotic episodes and causes for social maladjustment. With such information in hand one can critically re-interpret laboratory data. If, on reviewing these, an elevated or high normal blood cholesterol was discovered, one would be quite loath to make a diagnosis of hyperthyroidism.

BEHAVIOR OF THE CIRCULATION IN ESSENTIAL HYPERTENSION

In essential hypertension there is no increase in heat production. The peripheral blood flow is not increased and the cardiac output is normal or low.[11] The circulation time also is within normal limits unless decompensation is present.[12] Many patients develop anxiety states when they find that they have hypertension. Vasomotor instability appears and the metabolic rate is often elevated. In such cases one again must resort to a critical clinical study of the patient, repeated circulation times, and a study of the blood cholesterol values to arrive at a correct diagnosis. It is of course appreciated that patients with hypertension commonly develop hyperthyroidism. They will then show the diagnostic findings of hyperthyroidism.

FACTORS CONTRIBUTING TO CIRCULATORY FAILURE IN HYPERTHYROIDISM

Inadequate Nutrition of the Heart.—The magnitude of the energy expenditure in a patient with severe hyperthyroidism who has not received adequate treatment is not commonly appreciated. If we assume that a normal subject with a basal energy expenditure of 1,500 calories develops hyperthyroidism with a metabolic rate of plus 75 per cent, his basal expenditure will be 2,625 calories. If he leads a sedentary life, his requirements will be basal plus 30 per cent (3,412 calories). If he does moderate work they will rise to basal plus 50 per cent (3,937 calories). Plummer and Boothby[13] have noted that the "cost of work" is greater in hyperthyroid than normal patients. This is due not only to unnecessary movements but also to the greater than normal oxygen consumption required for a given task. The patient's movements are excessive due to the tremor and he often spends a good portion of the night in extra activity tossing from one side of the bed to another. It is, therefore, safe to say that a patient with a hyperthyroidism of this severity attempting to work will have an energy expenditure nearer to 6,000 to 7,000 than 4,000 calories. If such a patient should be exposed to a spell of hot weather with a relatively high humidity then he would be crippled in eliminating heat. Some of it would be retained and this would cause a further increase in his energy expenditure.

It is quite a problem for a man to eat 7,000 calories of food. In the first place, it cannot be secured in the ordinary diet without definite planning to include large quantities of fat. Hence, the probability that the uninstructed individual would select this amount of food is small. Further, the fatigue and exhaustion from which he is suffering would reduce his appetite and increase the gastrointestinal irritability to preclude the possibility of his eating that quantity of food. Consequently, the patient develops a sharp deficiency in his caloric intake, and a state of semistarvation is established. The inroads of starvation are grossly recognized by the disappearance in the fat stores, and the atrophy of the muscles. He develops a negative nitrogen balance and the urine is found to contain creatin. These findings indicate that a rapid destruction of muscle tissue is occurring. As soon as extra food is taken the creatin disappears and the negative nitrogen balance is converted into a positive one. The positive nitrogen balance will be maintained for a long time. This persistence of a postive nitrogen balance following adequate caloric intake is also seen in the convalescent period of many infectious diseases, notably typhoid fever and tuberculosis. The tachycardia in infectious diseases is unrelieved by drug therapy, but it is slowly relieved by rest and diets adequate in all respects. It would seem that a state of starvation has a deleterious effect on the heart muscle. In accord with this conception is the reduction in glycogen content of heart muscle occurring in experimental

hyperthyroidism.[14] Cowgill and his associates[15] reported that the onset of symptoms of B deficiency occurred more rapidly in dogs treated with thyroxin than in untreated ones. Since that time evidence has rapidly accumulated[16] that the hyperthyroid patient requires more thiamine than the normal subject, that he probably is somewhat wasteful in his use of it, and that its concentration in his liver is subnormal. The preoperative use of supplementary doses of thiamine in thyrotoxic patients is now a routine procedure in many clinics. Attention[17] has been called to deficiencies of other members of the B complex group in severely toxic hyperthyroid patients. That thiamine deficiency may be responsible for anatomic changes in the heart muscle is indicated by studies in pigs. Follis, Miller, Wintrobe, and Stein[18] have shown that their thiamine-deficient pigs die a cardiac death. They had labored breathing and cyanosis which was aggravated by exercise. Autopsy revealed edema of the lungs, cardiac dilatation, and focal necrosis in muscle fibers of the auricles and ventricles. In animals to which small amounts of thiamine were administered, widespread scarring of the musculature was observed.

CHANGES IN RATE AND RHYTHM

Tachycardia.—It is well known that an apparently normal heart subjected to a bout of paroxysmal tachycardia may develop failure as a result of the acceleration. During such periods of acceleration the output may be diminished as much as 33 per cent and at times the arterial pressure falls.[19] The filling of the ventricle is retarded by the short diastole and by the contraction of the auricle while the ventricle is still insystole. The decrease in diastole and the drop in aortic pressure renders the coronary circulation less efficient. Starling and Visscher[20] using the heart-lung preparation have shown that acceleration in rate diminishes the mechanical efficiency of the heart. In hyperthyroidism moderate increases in rate can be attributed to the increased blood volume and filling of the heart as described by Bainbridge.[21] In the faster tachycardias there are other factors operative, which cannot be regarded as physiologic. These are the increased thyroxin content of the heart muscle, and exhaustion. One can now appreciate the statistical reason for the poor prognosis in patients with excessively rapid heart rates. One should not indulge in optimism because of the absence of signs of failure. An elevated venous pressure is beneficial since it facilitates the filling of the heart and increases the cardiac output. These rapid hearts with normal venous pressures are quite vulnerable to acute failure. It is highly probable that sudden anesthetic deaths occasionally seen in hyperthyroid patients, who were apparently well compensated, are attributable to this mechanism.

Auricular Fibrillation.—A bout of paroxysmal fibrillation has a definite adverse effect on the heart. The cardiac output may be reduced as

much as 25 to 30 per cent,[22] due to the reduction in the blood contributed by the auricular systole. The venous pressure is normal and is unable to compensate for the auricular failure. The conductivity of the bundle of His is unimpaired and so the ventricular rate tends to follow that of the auricles. The diastole shortens, the heart muscle becomes fatigued, the coronary flow inadequate, and the pulse deficit greater. Fortunately one has available in quinidine a drug effective in restoring normal rhythm. This drug should be used promptly and given in doses sufficient to abolish the fibrillation. Conditions are somewhat different in patients with chronic fibrillation. They are frequently comfortable and may be oblivious of their cardiac irregularity. Their behavior is in sharp contrast to the uncomfortable and disturbed state of the patient with a bout of paroxysmal fibrillation. In chronic fibrillation there is usually cardiac decompensation of sufficient degree to elevate the venous pressure, which insures filling of the ventricles and compensates for the loss of auricular systole. In the elderly patient with arteriosclerosis there is already some impairment in conductivity of the bundle of His. The ventricular rate is correspondingly slowed and the pulse deficit is not so great.

Auricular Flutter.—The same situation prevails as in fibrillation. If the ventricles should follow the auricular rate a serious circulatory collapse would result because of the great reduction in cardiac output. Usually the refractory phase of the conducting tissues is longer than that of the auricle and thus a heart block with a 2 to 1, 3 to 1, or 4 to 1 rhythm is established. The reduction in the ventricular rate enables the heart to function reasonably satisfactorily. The paroxysmal attacks of flutter which occur postoperatively are most disabling and should be treated as emergencies.

It is much safer to treat flutter with digitalis than quinidine. Adequate doses of digitalis should increase the auriculoventricular block, slow the ventricle, and save the patient's life. It may convert the flutter into fibrillation by stimulation of the vagus. This shortens the refractory period of the auricular muscle, increases the transmission rate, and speeds up the revolutions of the circus wave, thus converting the flutter into fibrillation. When the drug is stopped the fibrillation is often replaced by a normal rhythm. Theoretically, quinidine should convert the flutter into normal rhythm by retarding conduction within the auricular muscle and increasing the refractory period. Practically this action is by no means certain and dependence should not be placed in it in such a grave emergency.

Heart Failure.—Heart failure is a complication that can be expected in patients with long-standing hyperthyroidism. When the severity of the hyperthyroidism is increased, failure appears more rapidly. The onset is usually slow and insidious. The factors leading to failure are operative on both the right and left heart. The clinical picture is that of congestive failure with dependent edema, large liver, and

other familiar signs. Not infrequently failure may be ushered in dramatically by a bout of auricular fibrillation. If the failure is chronic and confined to the left ventricle, the lungs will contain an increased volume of blood which moves slowly and is under increased pressure. The patient's symptoms will be those of cough, dyspnea, orthopnea, expectoration, and hemoptysis. The vital capacity will be reduced. The circulation time, arm to tongue, will be prolonged due to the slower movement of blood through the pulmonic area. The arm-to-lung circulation time (ether) will be normal. The x-ray plate of the chest will confirm the presence of pulmonic engorgement. At this stage the circulation time and vital capacity give objective evidence useful in evaluating the degree of failure.

When the right heart fails the cyanosis increases, the dyspnea decreases, and the signs of venous stasis appear. The venous pressure rises as the blood accumulates in the liver and dependent positions of the body. Its measurement becomes of clinical value during recovery only after the liver has returned to a normal size and the edema has disappeared.

Lahey's[23] experience has indicated that since the heart has failed as a result of overwork caused by the hyperthyroidism, one can exercise considerable latitude in operating on decompensated patients, since the removal of a part or all of the thyroid will reduce significantly the work of the heart. Numerous reports are in the literature of the feasibility of a therapeutic removal of the entire thyroid gland in patients with disabling cardiac disease. Pemberton[24] has reported the omission of digitalis in the treatment of all patients with hyperthyroidism except those who fail to compensate on bed rest. This practice was begun at the Mayo Clinic in 1923 at the suggestion of Plummer. As a result there has been a feeling in some quarters that it is probably unnecessary to establish preoperatively complete compensation in patients with hyperthyroidism. The medical service of the Research and Educational Hospital of the University of Illinois has made it a practice to accept and prepare for surgery all patients with hyperthyroidism who have severe cardiac involvement. As the result of such studies over a period of ten years the staff is convinced that a patient should be fully compensated and have some cardiac reserve prior to operation.

All the methods which are available for combating congestive heart failure should be used and in addition sufficient food should be furnished to meet the caloric requirements and to rebuild the depleted reserves of the body. As previously noted the requirements for vitamins, especially thiamine, are increased and these must be furnished in adequate quantities. Fluids by mouth or otherwise must be given in sufficient quantities to combat dehydration and to prevent storage of heat with a resulting rise in body temperature. All of these measures will be discussed elsewhere.

Oxygen should be used until the pulmonary engorgement is relieved. After a patient is well along toward compensation he enjoys being liberated from the oxygen. He will usually be quite comfortable in the day, but he will find difficulty in securing a night's sleep from which he wakens refreshed. This is an indication for the continuation of oxygen during the night. Sedatives and opiates will be required and should be given as needed.

Digitalis should be used in therapeutic doses, when heart failure exists. If the failure is associated with chronic fibrillation it is still the drug of choice. If heart failure is precipitated by a bout of paroxysmal fibrillation, then quinidine should be given, by mouth or per rectum (when vomiting is present), at frequently repeated intervals until the normal rhythm is restored. If restoration of normal rhythm is delayed by decompensation, then digitalis should be given in addition to the quinidine.

The edema of the tissues often disappears slowly under the best of treatment. Its increase is associated with an aggravation of the symptoms of dyspnea. Its decrease brings a corresponding relief. In patients with long-standing hyperthyroidism one should consider that there is a definite nutritional basis for the edema even though the serum proteins may be normal. The protein in the diet should be increased. The patient should then be given intramuscularly, on alternate days, 2 c.c. of liver extract (two units to 1 c.c.) and 50 mg. of thiamine chloride. The thiamine stimulates the appetite and corrects the thiamine deficiency. The liver extract seems to assist in correcting other deficiencies. Ammonium chloride alone or combined with an intravenous injection of one of the mercurial diuretics (at four-day intervals) should be given, providing there is no increase in the nonprotein nitrogen in the blood. In giving the mercurial diuretic it is well to dilute it with 10 c.c. of water or 5 per cent glucose solution. This avoids troublesome attacks of thrombophlebitis. When there is a retention of nitrogen one must proceed more cautiously. The retention of nitrogen may be due to passive congestion of the kidneys and it may disappear when the circulation is improved. While one is waiting for the oxygen, digitalis, and other measures to become effective, ammonium chloride alone can be given a trial. If the results are disappointing, then aminophyllin in 0.5 Gm. doses daily, dissolved in from 300 to 500 c.c. of 10 per cent glucose in distilled water, may be given slowly intravenously. The aminophyllin prevents the resorption of water by the tubules. However, its effect is not toxic and a damaged kidney does not become crippled further in its use as it does when a mercurial diuretic is administered. Aminophyllin dissolved in hypertonic glucose solution has a favorable effect on the pulmonary edema and the associated bronchospasm. Finally, the administration of the drug in a dilute form prevents annoying palpitation of the heart.

CRITERIA OF COMPENSATION

Enumeration of a Few Objective Criteria of Compensation.—The physical examination should show the absence of signs of decompensation.

Hidden edema should be removed. If present in the lungs, it predisposes to atelectasis and bronchopneumonia. Since it is customary to have the patient out of bed prior to his operation, this will afford an opportunity for the fluid to accumulate in the feet. The skin on the arms and other parts of the body feels thick when edema is present. In all cases the patient should be subjected to diuresis. This is done by weighing him daily over a period of time and collecting daily his specimens of urine. During this period he can be given ammonium chloride and a mercurial diuretic. The amount of diuresis and the weight variations will readily reveal the presence or absence of edema.

If the venous pressure is elevated one can be quite certain that the patient still has right heart failure. If the venous pressure is normal then the right heart is competent.

The arm-to-tongue circulation time should not be prolonged excessively. However, the circulation through the pulmonary spaces may be slowed without actual stasis. Consequently, one should not insist that this value be a normal one.

The final test of compensation is the vital capacity. If this has a value of 70 per cent or more one can feel that there is no pulmonary edema and that the expansion of the alveoli is not embarrassed. A vital capacity which is inadequate in a patient who otherwise appears in good condition can be improved by diuresis induced with ammonium chloride and a mercurial diuretic. If this is not effective a return to oxygen at night for a few days will often prove beneficial. One would not wish to create the impression that a patient may not be operated upon who has a vital capacity below 70 per cent. Obviously, clinical judgment and other studies will dictate the proper course to be followed.

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THE MEDICAL MANAGEMENT OF THYROTOXICOSIS

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IN RECENT years the control of thyrotoxicosis has been chiefly dependent upon three expedients: the use of iodine, exposure of the thyroid gland to x-ray, or surgical extirpation of a large part of the thyroid parenchyma. Although the approach has been by diverse routes, the therapeutic aims of all methods have been similar and the differences in effect have been quantitative rather than qualitative. Success in each instance has depended upon a diminution in the amount of circulating thyroid hormone with the expectation that thereby clinical manifestations of the disease would be minimized or removed.

Improvement has been evaluated by a number of criteria. The most emphasized has been a reduction in the basal metabolic rate which should be accompanied by a gain in weight, a diminution in the tachycardia, a decrease in pulse pressure, and amelioration of the abnormally high circulation rate. It is usually assumed that these symptoms are accompaniments of, or compensations for, the increased oxidative rate.

Improvement may also be evaluated by change in signs which are not so obviously dependent upon the degree of metabolic activity. Among these should be included the tremor, sweating, irritability, hyperkinesis, and exophthalmos. There should also be correction of the tendency to loss of nitrogen, calcium, and phosphorus from the body and an increase in the level of cholesterol in the plasma.

The muscular weakness which is so characteristic of chronic thyrotoxicosis should become less evident and with this benefit there should be an improvement in the spontaneous creatinuria, the inability to store ingested creatin and the abnormally high creatinin excretion which characterizes the disease.

The abnormality in creatin metabolism has been sufficiently constant to justify the use of spontaneous creatinuria and creatin tolerance tests as diagnostic criteria in cases which offer difficulty in differentiation between hyperthyroidism and psychoneurosis.[1] This has been especially useful since not infrequently the creatin defect has been evident when the basal is within normal limits. The tests have also been helpful in studying patients whose symptoms have not been satisfactorily controlled by thyroidectomy. Here again the creatin excretion may be excessive during periods when the basal metabolic rate is within the rather wide limits of normal.

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When the preceding criteria are used in evaluating therapeusis by means of iodine, radiation, or surgery, the results are similar in that all of the agents tend to ameliorate all of the disturbed functions. The mechanisms involved and the degree of benefit vary greatly. Apparently iodine exerts its influence by increasing the storage of active organic iodine compounds. The optimal benefits are temporary and alone seldom constitute a satisfactory means of control. Surgical operation accomplishes benefit by removing a large part of the mechanism which produces the hormone. Considering the fact that the amount to be removed must be determined by guess, subtotal thyroidectomy has been, and is, a surprisingly satisfactory procedure. Radiation is effective because of injury to the structure of the gland or of a temporary diminution in its function. While radiation has been in the past less helpful than surgery the possibilities of newer applications in the form of radioactive iodine have not been sufficiently explored. Hertz and associates[2] and Hamilton[3] have shown a selective action of radioactive iodine in hyperplastic portions of thyrotoxic glands and, in a few cases, have obtained by its use encouraging therapeutic results.

Another mechanism of reducing the production or delivery of thyroid hormone should be mentioned although it can not be feasibly employed in treating hyperthyroidism. The ablation, destruction, or loss of the anterior lobe of the pituitary removes the stimulus to functional thyroid activity. Results are a small thyroid gland in which the cells are atrophic and simultaneously a great reduction in the level of circulating thyroid hormone. In this state the thyroid gland is by no means destroyed and for at least a considerable period its function can be restored by appropriate stimulation with the thyrotropic hormone of the pituitary.

Still another method by which the amount of thyroid hormone may be reduced has been shown by Means and others[4] in the hyperplasia of the thyroid gland and the paradoxical hypothyroidism which follows the administration of thiocyanate, and which is prevented by the administration of iodine.

Of the expedients which have been available in the treatment of thyrotoxicosis, partial surgical ablation of the thyroid gland has offered most hope. With the best preparation and in the hands of excellent surgeons the operative risk has been diminished to less than 1 per cent with recurrence of clinical hyperthyroidism in only 10 to 15 per cent of the patients operated upon. This remarkable record can be attributed only in part to increase in surgical skill. Better understanding of thyrotoxicosis and appropriate emphasis upon control of physical activity, freedom from emotional strain, iodine, and adequate diet have contributed significantly to successful management. While all of these factors are important in any phase of treatment they have been used more in preparation for operation than as ends in themselves.

CONTROL OF PHYSICAL ACTIVITY

If partial thyroidectomy is contemplated, a thyrotoxic patient should be under constant observation and preferably in a hospital for at least two weeks preceding the operation. Effective rest and relaxation are necessary in the treatment of hyperthyroidism. The thoroughness with which they must be enforced, however, varies with the age and the general condition of the patient as well as with the degree of thyrotoxicosis. The young previously healthy individual has such large factors of safety that even hard work and the unmodified stress of life may cause no obvious distress. The effects of fatigue, however, are cumulative and strains which do not make their effect evident at once may cause later trouble. It should be the rule to spare the hyperthyroid patient all unnecessary stress until his condition can be permanently remedied. While this is, to a certain extent, optional in the younger individual, it becomes obligatory in those whose hearts have lost, with the passage of the years, some of their initial reserve or in those in whom the degree of hyperthyroidism threatens the occurrence of a crisis. It applies to all thyrotoxic patients during infection or subsequent to psychic or physical trauma.

Appropriate relaxation is by no means easy of accomplishment. In many ambitious, restless, thyrotoxic patients complete inactivity is out of the question and attempts to enforce it in the solitude of darkened rooms, or in other respects too literally, may be among the principal causes of failure in medical management. Recumbency is by no means essential. In the most severe cases, when strict bed rest is necessary, the bed should be adjusted frequently by the attendant so that the patient may assume the most comfortable position for each permitted activity. Even in the very ill, the avoidance of boredom is more important than complete quiescence. Activities may be prescribed according to the taste of the patient and may include short periods of reading, listening to the radio, visiting, or performing some of the simpler, easier tasks offered by occupational therapists. In prescribing activity, strict limits must be placed on the time allowed for each item and it must be emphasized that there is no obligation to complete any task.

Periods of complete rest and relaxation should be frequent but need not be prolonged except in those whose hearts are seriously incompetent. In the less severe cases much more liberty is permissible as long as its effect can be accurately observed. Indeed, in the preoperative period the effect of walking on pulse, blood pressure, and respiration may offer a valuable indication as to the ability of the patient to withstand the strain of the operation.

REASSURANCE

Too much emphasis cannot be placed on psychologic factors in the management of thyrotoxicosis. Patients are irritable, excitable, restless,

and hyperkinetic but usually are astonishingly free from imaginary fears. On the other hand they are susceptible to suggestion and are influenced to an unusual degree by the mood of a physician. An attitude of gloom or uncertainty may be disastrous while optimism and assurance often have dramatically beneficial effects. As soon as acquaintanceship has been established, the main characteristics of the disease may be detailed to the patient. Emphasis must be placed on curability but also on the fact that the complete recovery may require time and that arrangements must be made for a prolonged period of inactivity. Helpfulness concerning these arrangements goes far in reassuring the patient. Thyrotoxic individuals who show no undue anxiety over their physical condition may become dangerously disturbed when they contemplate the consequences of illness on their financial security or on their dependents. While formal attempts at psychotherapy may be quite inadvisable during the preoperative period, an understanding of factors and problems which prevent relaxation is essential. Even when the causes of worry can not be removed, a sympathetic and helpful attitude on the part of the physician exerts a significant therapeutic effect.

In most cases the question of operation can be discussed quite fully. Emphasis should be laid upon the relatively slight risk of operation and the relatively high incidence of resultant permanent cure. It is also important to emphasize that operation will not be attempted if the risk is great. The operation can be represented as a goal which the patient may achieve if he can relax enough and can establish a satisfactory state of nutrition.

CONTROL OF RESTLESSNESS

Restlessness may interfere seriously with treatment during the preoperative period. Its control will depend in large part upon reassurance, the prevention of boredom, and a thorough understanding of the patients' problems and attitudes. In some cases, however, restlessness and insomnia persist in spite of the most intelligent management. In such cases morning sponge baths at a temperature of about 80° F. and evening sponge baths at a temperature of from 90 to 95° F. may be helpful. For those who are less ill, an evening tub bath at a temperature of from 98 to 100° F. may be prescribed as a means of combating sleeplessness. An ice bag over the heart and over the thyroid gland may be used as a measure of subjective relief in those who are made restless by palpitation. While thyrotoxic individuals are not often unduly disturbed by sounds and lights, protection by isolation may be indicated for individual patients.

When restlessness can not be controlled by such simple measures, phenobarbital may be given in doses of from 15 to 30 mg. four times each day. If insomnia is a troublesome factor the night dose may be

increased to 60 or even to 90 mg. or a comparable dose of a shorter acting barbiturate such as pentobarbital may be tried. Both paraldehyde and chloral hydrate are at times useful as temporary substitutes for the barbiturates. Large doses of sedatives are seldom if ever indicated and may cause confusional states which are difficult to control and occasionally dangerous.

DIET

Undernutrition often plays an important role in chronic thyrotoxicosis. With maximum relaxation a thyrotoxic patient with a basal metabolic rate of plus 60 is expending as much energy as a normal person would require to sweep a floor. This activity must be maintained day and night and day after day. Moreover, all muscular work is performed inefficiently. Accurate observations have indicated that in performance of a given task thyrotoxic patients require approximately 40 per cent more energy than a normal person.[5] Roughly the caloric requirement during bed rest in such a degree of thyrotoxicosis may be calculated to be at least twice normal.

In hyperthyroidism there is always a tendency to depletion of glycogen which is demonstrable in the liver and may be a significant factor in the heart muscle and other tissues. For this reason a high carbohydrate intake is advisable. Excessive amounts of fat, on the other hand, are undesirable because they tend to produce diarrhea. An allowance of 1 Gm. of protein per kilogram of body weight is usually sufficient to prevent nitrogen loss if a sufficient caloric intake is maintained. Larger amounts may be regarded as somewhat undesirable because of the relatively high specific dynamic action of protein.

All thyrotoxic patients tend to lose calcium and therefore to require more than the normal intake of lime salts. The observations of Cowgill and Palmieri[6] have shown that the requirements of thiamine are proportional to the amount of food metabolized. This suggested at once that disturbances in thiamine metabolism might develop in thyrotoxicosis, and the work of Means and associates,[7] and Williams and others[8] has demonstrated that the administration of thiamine is of distinct advantage as an adjunct in the treatment of thyrotoxicosis. More recently, Drill and Overman[9] have shown that during experimental hyperthyroidism an increased intake of pyridoxine and pantothenic acid is required in order to maintain normal nutrition.

These factors must be taken into account in prescribing a diet during the preoperative period or at other times in the treatment of hyperthyroidism. For a small girl weighing 110 pounds, a diet containing carbohydrate 300 Gm., protein 50 Gm., and fat 275 Gm., would represent a satisfactory approximation at the beginning of treatment. This should include the use of one quart of milk each day and should be reinforced by the daily administration of from 10 to 20 mg. of thiamine hydro-

chloride and yeast or other vitamin supplements which will increase materially the usual intake of pyridoxine and pantothenic acid. Since the caloric needs of each patient can not be calculated exactly, daily weight must be used as the best indication of the sufficiency of any given diet.

IODINE

Appropriate use of iodine has saved the lives of thousands of thyrotoxic patients and since 1923[10] has been regarded as essential in the preoperative treatment of Graves' disease. Its beneficial effect depends upon the specific need of the thyrotoxic individual and when the need has been satisfied by increased intake the administration of larger amounts results in no perceptible added benefit. In thyrotoxic patients who have received no iodine other than that contained in a usual diet, the exhibition of the drug results in a characteristic and usually predictable response. This may be discernible in twenty-four hours, obvious in three or four days, and maximum in ten to fourteen days. Rather dramatic improvement in the clinical manifestations of Graves' disease is accompanied by changes in the structure of the thyroid gland. Continued use of iodine may or may not be accompanied by intensification of thyroid symptoms. Discontinuance of iodine on the other hand is followed by a gradual ascent of the basal metabolic rate to its previous level and by an increase in thyrotoxic symptoms to a severity which approximates that obtaining before iodine was given. About 3 per cent[11] of patients with Graves' disease do not respond to iodine.

The amount of iodine required to produce an optimal response is small and may vary between 6 and 15 mg. per day in different individuals with Graves' disease.[12] Many compounds containing iodine are known to be effective and the response seems to be equally favorable from inhalations of ethyl iodide and from oral administration of diiodotyrosine, potassium iodide, hydriodic acid, or Lugol's solution.[11] One cubic centimeter of syrup of hydriodic acid containing about 13 mg. of iodine, or 2 minims of Lugol's solution containing approximately 18 mg. of iodine should be all that is required for each day's treatment.

Ordinarily it is calculated that the optimum effect of iodine should develop in from ten to fourteen days following its first exhibition. This should not be taken too literally. It is the condition of the patient and not the interval that must determine the time of operation.

USE OF DIGITALIS

The state of the circulation during the preoperative period must be carefully observed. Tachycardia and moderate grades of cardiac incompetence are best controlled by rest and iodine. Digitalis is indicated whenever there is obvious congestive heart failure or in cases of auricular fibrillation with very rapid pulse rate or continued or large pulse deficit. In such cases the drug should be started early in the preoperative

period in order that its benefits may be achieved and its possible toxic effects controlled before the time of operation. Statistical evidence indicates that the routine administration of large doses of digitalis is detrimental and actually increases the mortality from surgical procedures. Tachycardia with regular rhythm and without cardiac decompensation is never an indication for the use of digitalis.

INDICATIONS AND CONTRAINDICATIONS FOR OPERATION

After two weeks of controlled activity, psychotherapy, iodine administration, and dietotherapy it is hoped that a patient will be in sufficiently good condition to justify subtotal thyroidectomy. Not all cases can be so managed. Certain contraindications should be mentioned. It has been noted that those who respond unsatisfactorily or not at all to iodine have a relatively high operative mortality. A rising metabolic rate after an initial favorable response should also be viewed with some apprehension. A basal metabolic rate higher than plus 40 is usually regarded as unfavorable although it must be emphasized that basal rates are to be evaluated in relation to other clinical manifestations. Failure to maintain weight with or without vomiting or diarrhea during the preoperative period is to be regarded as an unfavorable sign and often a contraindication to immediate operation. The coincidence of infection of any sort, acute worry, grief, emotional storms, and psychoses increase the risk to such an extent that immediate operative procedures cannot be considered. Old age in itself is not a sufficient reason for depriving a patient of the benefits of thyroidectomy but accompanying degenerative diseases may in many cases render any thyroid surgery somewhat futile. Congestive heart failure which has been uncorrected by rest, iodine, and digitalis may preclude any immediate operation. In deciding about such cases, however, it must be remembered that thyroidectomy is often followed by almost complete recovery even from rather advanced failure. For this reason, repeated effort by all therapeutic methods should be made to attain temporary improvement which may permit operation.

NONSURGICAL MANAGEMENT OF CHRONIC THYROTOXICOSIS

Those patients who for one reason or another cannot be subjected to subtotal thyroidectomy must be treated by other methods. In the nonsurgical management two factors are perhaps outstanding. The first is that the condition of thyrotoxicosis undergoes wide spontaneous fluctuations in severity with periods of remission and relapse which are more or less obviously influenced by emotional states and infections, as well as by the menstrual cycle and pregnancy. The second is that the administration of an appropriate amount of iodine modifies the extent of the fluctuations and usually prevents the serious consequences of acute hyperthyroidism during relapse. These characteristics indicate

the importance of protection from those factors which may be preventable, and the advisability of continuous use of such small amounts of iodine as are necessary to maintain an optimal state of the thyroid gland.

With the best management, however, results have not been very satisfactory. While remissions with periods of moderately good health have been common, cure in the sense of removing the tendency to relapse has been decidedly rare. Moreover, the continuance of even a moderate degree of hyperthyroidism produces circulatory strain which, with advancing years and diminishing cardiac reserve, produces obvious thyrotoxic heart disease. In such cases the persistent cautious use of x-ray has resulted in much benefit and has proved itself next to operation the most potent weapon in the permanent control of the condition.[13]

THIOURACIL

Although the results of surgery have been brilliant indeed and although the x-ray has been instrumental in the successful control of many cases, it is apparent that all of the present means of treating thyrotoxicosis leave much to be desired. None achieves the ultimate goal of a therapeutic agent which without mutilation, destruction, or disturbance of function of other organs can check the production or prevent the delivery of excessive amounts of thyroid hormone.

Interest in the possibility of finding a more ideal agent was stimulated by the discovery of the McKenzies and McCollum[14] that prolonged administration of sulfaguanidine produced hyperplasia of the thyroid gland which, like thiocyanate, decreased the basal metabolic rate to levels approaching myxedema. Unlike thiocyanate, the effect could not be prevented by iodine. On the other hand its action might be obviated by giving thyroxin. The work of the McKenzies was extended by Richter and Clisby[15] and by Kennedy[16] to show that an effect similar to that of sulfaguanidine could be produced by compounds containing the thioureylene radical and particularly by thiourea and its derivatives. Extensive studies by Astwood[17] with over 100 related compounds revealed that the most marked effects could be obtained with thiouracil. In animals Astwood was able to show that glands subjected to prolonged administration of thiourea and its derivatives became enlarged with follicles irregular in shape, containing scant colloid and lined by columnar cells with large nuclei and numerous mitoses.[18] The administration was followed after a short interval by a lowering of the basal oxygen consumption, a decrease in growth, and a diminished food intake. The obvious question whether these substances would have an effect in human thyrotoxicosis was approached by Astwood and by Williams and Bissell.

Astwood[19] treated two patients, one of whom received thiourea and the other thiouracil. In both there was a fall in metabolic rate and

an increase in body weight. The more extensive studies of Williams and Bissell[20] concerned nine patients who were treated with thiouracil. All had had typical manifestations of thyrotoxicosis over periods from six months to twenty-two years. In most instances the thyroid glands were enlarged. Initial basal metabolic rates ranged from plus 36 to plus 88. In all cases the basal had returned to normal with an average of plus 1 for the group within from three to seven weeks following institution of treatment. In four weeks there was a decrease in the protein-bound iodine of the plasma to normal or below. Williams showed also that administration of thiouracil did not interfere with the predicted effect of 1.5 Gm. of desiccated thyroid in two cases of myxedema. His observations confirmed animal experiments which indicated that thiouracil does not interfere with the action of preformed thyroxin.

These preliminary observations showed the remarkable effect of thiouracil on the basal metabolic rate. From both theoretical and practical standpoints it was of great interest to inquire whether the fall in oxidative rate was accompanied by the changes which are ordinarily employed as criteria for good therapeutic results from iodine, radiation, or surgical treatment. The question was pertinent since it is well known that the variations in basal metabolic rate encountered in fever, in leucemia, in Addison's and Fröhlich's diseases, and in dinitrophenol poisoning are not necessarily accompanied by other metabolic and circulatory changes which characterize variations in activity of the thyroid gland. It would not be impossible that the effect of thiouracil on oxidative rate might be accomplished by some mechanism other than by diminishing the amount of circulating thyroid hormone.

Observations made by Sloan and Shorr[21] demonstrated that thiouracil produces changes in circulation rate, pulse rate, blood pressure, calcium and nitrogen balance, creatin metabolism, and cholesterol levels which were qualitatively identical with those achieved by the successful use of iodine, x-ray, or thyroidectomy. The effects of the drug are physiologic in the sense that it tends to correct those functions which are disturbed or exaggerated in thyrotoxicosis.

The effects of thiouracil are now being studied in many clinics. It has been found in the great majority of cases of Graves' disease that freedom from thyrotoxic symptoms may be attained by a few weeks of intensive treatment with thiouracil and that essentially normal conditions may be maintained indefinitely by administration of small amounts of the drug. It has also been shown in a few cases by Astwood[22] that withdrawal of the drug after six to nine months of treatment does not result in recurrence of thyrotoxicosis. Unfortunately, it has also been found that thiouracil possesses toxic properties. Granulocytopenia, early noted by Astwood,[19] has resulted in several deaths, one of which has been reported.[23] Use of the drug has also been followed not infrequently by eruptions[2] and by periods of pyrexia.[24]

It is too early to predict whether thiouracil can be employed safely in the routine management of thyrotoxicosis. Present evidence is not sufficient to exclude possible hidden toxic reactions which might result from its continued use. At the moment its employment should be restricted to cautious administration in well-selected cases under constant observation. It may not be too much to hope, however, that there will be found closely related drugs which possess its favorable actions without its toxic side effects.

SUMMARY

Medical treatment of thyrotoxicosis has found its rationale in our present concepts of its nature. It is based first on the understanding that the disease is aggravated by infections, by physical and emotional stress, and by such variations in function of the endocrine system as occur at the time of puberty and during menstruation and pregnancy; second, on the observation that relapses may be modified or minimized by the administration of relatively small amounts of iodine. Adequate diet, reassurance, control of activity and of restlessness, protection against infections and against physical and psychologic trauma, and the feeding of small amounts of iodine have constituted the mainstays of medical treatment. These expedients have been used chiefly as a preparation for surgery or when this has been impossible as ancillary to cautious, persistent application of x-rays. When used by themselves they have not been successful in curing or controlling effectively many cases of thyrotoxicosis.

The recent introduction of thiouracil offers new hope of more effective medical control and suggests the possibility that the use of thiouracil or related compounds may permit nonsurgical treatment in a large number of thyrotoxic patients.

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CHEMOTHERAPY IN HYPERTHYROIDISM

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THERE have been extensive clinical trials of a variety of substances with the aim of controlling states caused by overactivity of the thyroid gland.[1] These have been concerned mainly with attempts to inactivate or to neutralize the circulating thyroid hormone or to suppress its production in the thyroid gland. The proposed agents have been classed as "antithyroid substances," although there was often no clear statement of the mechanism by which they were thought to act. One of the first such substances to receive considerable attention was called "antithyroidin," a preparation made from the serum of thyroidectomized animals. Other agents have included various extracts of human and animal blood and tissues, of the serum or urine of animals which had been treated for long periods with various thyroid hormone preparations, and of the urine of patients with various diseases. A miscellaneous group of organic compounds such as various fats, sugars, and vitamins have also been proposed as having therapeutic value in hyperthyroidism. Among the many inorganic compounds such as salts of the heavy metals and halogens which have been explored, iodine remains as the most widely used therapeutic agent for thyrotoxicosis. None of the other substances has come into general use for, in most cases at least, there was little sound rationale for their introduction as therapeutic agents.

GOITROGENIC AGENTS

The recent development of chemical compounds effective in inhibiting the synthesis of thyroid hormone dates from studies on the mechanism of action of various goitrogenic agents.

Although it had long been known that various substances would cause thyroid enlargement in animals, the mechanisms involved were not exhaustively investigated. In many instances it was established that the goitrogenic action in question could be prevented by iodine, and the view became current that most of the so-called goitrogenic effects operated through a deficiency in iodine.

Recently there were reported from three laboratories, almost simultaneously, new types of goitrogenic agents. Mackenzie, Mackenzie, and McCollum[2] found that sulfaguanidine when fed to rats for short periods of time induced a marked enlargement and hyperplasia of the thyroid gland, an effect that was not inhibited by iodine. Richter and

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Clisby[3] showed that phenylthiourea was goitrogenic and Kennedy, Purves, and Griesbach[4] described in detail the goitrogenic action of rape seed—an effect which Kennedy[5] later attributed to allyl thiourea, a possible constituent of rape seed. Detailed studies on the mechanism by which sulfonamides and thiourea induce thyroid enlargement led to the concept that the goiter is compensatory in nature and that the primary action of such compounds is the inhibition of thyroid hormone synthesis.[6,7] This finding suggested that compounds related to the sulfonamides or thiourea might be useful therapeutic agents and consequently the activity of a large number of such compounds was explored.

It was found that the coumpounds tested could be divided into three classes: thiourea derivatives, those containing an aminobenzene grouping, and the thiocyanates.[8] The thioureas on the whole were the most active and among these thiouracil had the highest activity. The aminobenzene derivatives included the common sulfonamides of which sulfadiazine was the most active. The thiocyanates were distinct from the other two classes in requiring a diet low in iodine; the goitrogenic action was completely inhibited by added iodide. Furthermore Rawson, Tannheimer, and Peacock[9] have shown that the thiocyanate goiter readily takes up radioactive iodine while the enlarged glands resulting from thiouracil administration do not. The only difference thus far found between the first two groups is one of species difference. The aminobenzene derivatives are without effect when administered to chicks,[6,10] whereas various thiourea derivatives are highly effective in this species.[10,11]

On the basis of these observations some of the early work on goitrogens may offer an explanation. Thus, it is tempting to speculate that the goiter produced in rabbits from the feeding of cabbage described by Chesney, Clawson, and Webster,[12] and by Marine and Baumann,[13] as it was completely prevented by iodide,[14] may have resulted from thiocyanates present in the cabbage acting in the presence of a diet which must have been very low in iodine.

Similarly, Purves[15] has recently shown that the goiter produced in rats by feeding rape seed is partially but not completely inhibited by iodide. This may indicate that there are two types of goitrogens present in rape seed, one a thiocyanate inhibited by iodine and the other a thiourea derivative not inhibited. The finding of Marine and associates[16] that the goiter induced by acetonitrile in rabbits is completely inhibited by iodine might now be interpreted in a similar way. Cyanide is known to be converted to thiocyanate in the body as a means of detoxication and it may have been the thiocyanate formed which was responsible for the effect upon the thyroid gland.

In any case it is apparent that the action of cyanides and thiocyanates is inconstant and, being dependent upon low levels of iodine intake, is difficult to control. Studies on goitrogens are thus more readi-

ly performed on the aminobenzene derivatives or on compounds related to thiourea, preferably the latter, which do not appear to suffer the disadvantage of marked species differences.

TREATMENT OF THYROTOXICOSIS

Thiourea.—In view of the finding in animals that the formation of thyroid hormone is inhibited by relatively nontoxic compounds it seemed of interest and importance to determine whether the excessive production of hormone in human thyrotoxicosis could be checked by the administration of one of these agents.

The first compound to be tested clinically was thiourea, a compound which appeared to be particularly nontoxic in animals. During the early part of 1942 several normal and two hyperthyroid individuals were given from 1 to 2 Gm. doses of this compound for several days. No toxic effects were noted and there was no immediate change in the metabolic rate. When treatment was continued for several weeks, improvement of thyrotoxic symptoms and a satisfactory response of the basal metabolic rate were observed.[17]

This effect of thiourea was confirmed and extended by the studies of Himsworth,[18] who treated six patients with hyperthyroidism with good results. Thiourea was found to be unpleasant to some persons because of the aftertaste and because of the unpleasant odor that was imparted to the breath. Himsworth found that some of his patients experienced nausea and vomiting. In the first case referred to, treatment had to be discontinued because of the development of a skin rash. This complication is apparently quite common with thiourea as it has subsequently occurred in a number of patients treated with adequate doses. A recent note also records the occurrence of granulocytopenia and thrombocytopenia[19] in a patient treated with thiourea. Although a number of investigators have studied the effects of thiourea in hyperthyroidism and will doubtless publish their results shortly, its activity appears to be too low and the incidence of a toxic reaction too high for it to be recommended as a useful drug.

Thiouracil.—Shortly after the first successful trials with thiourea had been initiated, a study of the activity of a number of related compounds revealed that thiouracil was a more highly active substance.[8] Most of the studies to date on the chemotherapy of thyrotoxicosis have been confined to this drug, which on the basis of recent work appears to have an activity approximately ten times that of thiourea on a weight basis; molecule for molecule, thiouracil is thus seventeen times as active as thiourea.

When thiouracil was tested in clinical hyperthyroidism its high activity was soon apparent. A total daily dose of from 0.2 to 0.6 Gm. was found to be effective in controlling the symptoms of hyperthyroidism and in reducing the basal metabolic rate to normal.[17] In one case a dose of 2 Gm. daily resulted in the production of a severe but not

fatal case of agranulocytosis. Although unfortunate, this event has served to show that caution and close observation are essential when this drug is being given.

To date, an impressive series of cases has been treated with thiouracil both in this country and abroad, and sufficient information is now available from published and unpublished reports to form the basis for a preliminary opinion on its usefulness in the routine treatment of hyperthyroidism.

The first published confirmation of the clinical effectiveness of thiouracil was that of Williams and G. Bissell[20] who treated nine patients with doses of about 1 Gm. daily. Hyperthyroidism was adequately controlled and no serious toxic manifestations were noted. Several minor side effects were attributed to the drug including edema, elevated serum chlorides, and swelling of the salivary glands. Similar doses were used by Palmer[21] in the treatment of twelve patients with equally satisfactory results and no definite toxic effects. However, Gabrilove and Kert[22] have recently indicated that doses of this order of magnitude are not safe since three out of nine treated patients showed toxic manifestations, two consisting of fever and one of leucopenia. No further cases of agranulocytosis have yet been published but apparently it is common experience to notice a fall in the granulocyte count during treatment. Welshman[23] has recorded two such cases in which it was considered necessary to discontinue treatment. However, in some cases this fall is temporary and the normal blood picture returns during continued treatment; some degree of leucopenia is frequently noted in hyperthyroidism when no drug is given. Rawson and his collaborators,[24] using a daily dosage of 0.6 Gm. or less, have recorded the successful treatment of twenty-five patients without toxic effects and demonstrated that surgery can be safely performed on patients who have been brought to normal by thiouracil treatment. By the use of radioactive iodine and by assays of the treated glands they have provided further evidence that thyroid hormone synthesis is inhibited by thiouracil.

A more common side-effect of the drug has been noted recently.[25] Of a total of forty-eight persons given the drug, four developed a febrile reaction on the ninth to eleventh day of treatment. When the drug was withdrawn the fever subsided and in three of these a subsequent test dose was followed some hours later by an abrupt rise in temperature. Three received a daily dose of 0.6 Gm. and one, 0.4 Gm. suggesting that these are instances of true idiosynerasy.

The dosage most commonly employed in recent cases has been 0.4 Gm. daily in two doses of 0.2 Gm. each at twelve-hour intervals. Larger doses and a further subdivision of the daily dose do not appear to be more effective. As little as 0.2 Gm. daily in two doses has been effective and in only two cases did it appear that 0.3 Gm. daily was inadequate. Currently, a dose of 0.6 Gm. daily is given only to large

individuals and to those in whom a slow response is anticipated. Since this lower dosage has been used there have been no toxic reactions except the four instances of fever noted.

According to the observations made in this clinic, the details of which have recently been published,[27] the usual pattern of response of previously untreated cases of Graves' disease is as follows. When an adequate control period of rest in bed and sedation is allowed before thiouracil is begun, an estimation of the rate of response to it can be obtained by frequent determinations of the basal metabolic rate. In some instances a distinct drop in the metabolic rate was observed in as short a time as three days, but usually a week of treatment was required before one could be sure that a distinct effect had been obtained. It is possible, however, that had the control period been prolonged a somewhat lower base line would have been reached before therapy was begun and this would tend to lengthen the apparent latent period of the therapeutic response. Once the metabolic rate had begun to fall it continued to decline in a fairly regular manner for the next week or ten days and then exhibited considerable individual variation. In some cases the response continued rapidly and the metabolic rate reached normal levels within two weeks. On the average, however, three weeks were required before the metabolic rate became normal. In many cases the metabolic rate, after falling to near normal, continued at a slightly elevated level or temporarily increased somewhat before exhibiting a second decline to normal or subnormal values.

Clinical improvement seemed to parallel quite closely the fall in metabolic rate. Sometimes subjective improvement was claimed before there were any objective signs of a therapeutic effect but an evaluation of this phenomenon is not at present possible. Other indices of improvement which paralleled closely the metabolic response were weight gain, slowing of the basal pulse rate, and a decrease in tremor. After the metabolic rate had reached normal most of the symptoms and signs of hyperthyroidism had disappeared. In most instances muscular weakness was the last symptom to clear and usually it continued until after the normal body weight had been regained.

Exophthalmos was not obviously influenced during the first few weeks of treatment. Coincident with the decrease in metabolism there was a decrease in the stare which may have been responsible for the apparent regression of proptosis, but only after several months could one be sure that the exophthalmos was indeed decreased. Thus far no increase in the degree of proptosis has been apparent but accurate measurements were not made. Malignant progression of exophthalmos has not yet been encountered.

The size of the thyroid gland has been noted to change in a rather irregular manner during therapy. In those patients with small glands before treatment was started it appeared that the glands became small-

er during treatment. However, accurate estimates of size in such cases are difficult and are complicated by changes in the consistency or firmness of the gland. Under thiouracil treatment the thyroid was noted to become softer, in fact in some cases this made it impossible to determine the borders and outline of the thyroid. In patients with initially small glands this factor would then give the erroneous impression of a decrease in size and in some cases the softness made the gland impalpable. Changes in size were more definite in those exhibiting large diffuse goiter prior to therapy. In most of these there was an unquestionable increase in size during the first few weeks of therapy and an increase in the signs of hyperemia. Later on the gland slowly regressed and in some the thrill and bruit, previously very striking, entirely disappeared. In two cases the addition of a small dose of iodine to the thiouracil treatment seemed to be responsible for a sudden cessation of the bruit and a decrease in the size of the gland. In these two instances the metabolic rate fell precipitously coincident with the giving of iodine, in one it fell from normal to a level of -25 per cent in the course of a few weeks although only a small maintenance dose of thiouracil was being given.

The course of the therapeutic response as just described has been found to be quite uniform in most cases of primary hyperthyroidism. Three patients with typical Graves' disease exhibited a greatly delayed response to thiouracil and the only factor common to each was the prior administration of full doses of iodine. Presumably iodine therapy tends to cause the deposition of large stores of thyroid hormone within the gland; if the current concepts of the manner of action of thiouracil are correct, then these delayed responses become intelligible. As previously suggested,[17] the major portion of the stored hormone must become exhausted before an effect upon the metabolic rate can be achieved. The action of the drug is to block the formation of new hormone and it is without effect on the release or the activity of the hormone stored within the thyroid gland. It has consequently been the recent practice to discontinue iodine, if it has been given, for some weeks prior to starting thiouracil therapy.

Long latent periods have also been noted in several instances of toxic nodular goiter and in these, as in the iodine-treated cases of Graves' disease, there is presumably a large amount of hormone-containing colloid within the gland, and presumably the same mechanism is operative in causing a delayed response. This factor is apparently also responsible for the fact that in persons with normal glands a prolonged period of treatment is required before a fall in the metabolic rate occurs. In the normal individual there is a large store of hormone and the time required for the gland to become depleted is further extended by the fact that the rate of release of hormone is much slower than in the case of the overactive glands of hyperthyroid individuals.

Remission.—In the first few treated patients therapy was withdrawn shortly after the metabolic rate had reached normal in order further to establish that the observed effect was attributable to the drug. It was apparent from these tests that all the manifestations of the disease returned promptly when the treatment was discontinued and that no lasting improvement could be obtained from short periods of medication. In subsequent cases the treatment was continued for an arbitrary period of from six to eight months in dosages that maintained a normal or somewhat subnormal metabolic rate. During this period the patients remained free of symptoms and appeared normal in every way with the exceptions of continued eye signs and thyroid enlargement in some cases. At some time during this period of treatment a spontaneous remission presumably occurs but as yet no means has been found to determine when this takes place. Of the twelve patients who have thus far completed such a course of therapy and from whom the drug has been withdrawn, nine have been under close observation for from two to six months. In each case the metabolic rate has remained normal, body weight has been maintained, and no symptoms of hyperthyroidism have appeared.[26] As the effect of the drug could be expected to subside within a few days after the last dose, it must be presumed that remissions occurred. Thus far there is no experimental basis for the assumption that the thiouracil was responsible for the remissions, and it is more reasonable to suppose that the drug merely controlled the disease and maintained a state of health which permitted a spontaneous and apparently complete recovery to occur.

DISCUSSION

There remains little doubt that thiouracil and related compounds can effectively and perhaps completely block the synthesis of thyroid hormone. Administered to hyperthyroid patients the value of such drugs as therapeutic agents can scarcely be questioned. Advantages over other forms of therapy include the avoidance of surgical operation, the reproducible nature of the response, the lack of any evidence of the development of tolerance or refractiveness, and ease with which the metabolic rate can be controlled at any desired level.

The main disadvantage of this form of therapy is the occurrence of toxic reactions in a certain small percentage of cases. The use of small doses and further investigations into the nature of the toxic effects may help to reduce the incidence or severity of such reactions. As thiouracil is only one of a number of active compounds it seems quite likely that equally active substances which are productive of fewer reactions may be discovered. Until such new drugs are developed there seems to be no cause to restrict the use of thiouracil in the treatment of thyrotoxicosis. Dangerous toxic reactions are apparently quite rare; the more common reactions may be such that treatment

has to be discontinued but in such instances nothing has been lost. The subsequent response to iodine remains unaffected and surgery can be performed when necessary without added danger.

Another drawback to this treatment involves its possible effect upon the size of the thyroid gland. Individuals with very large goiters may experience a further growth of the gland which could result in symptoms from pressure on adjoining structures. The current practice of removing large goiters for cosmetic reasons or because of pressure symptoms and removing nodular goiters because of the possibility of neoplastic changes is probably sound. The possibility of using thiouracil as a means of preparing such cases for operation is being explored in a number of clinics.

SUMMARY

Many substances have from time to time been proposed as remedies for hyperthyroidism, but with the exception of iodine none has been generally accepted.

A brief review of the origin of effective chemotherapeutic agents for thyrotoxicosis and a summary of some of the clinical data thus far available indicate that compounds such as thiouracil are effective in the treatment of this disorder. Serious toxic reactions are rare and the ease with which the disease can be controlled recommends this form of treatment. The frequency of spontaneous remission during therapy indicates that lasting therapeutic effects may be anticipated.

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FACTORS INFLUENCING OPERABILITY AND MORTALITY RATE IN GOITER

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AS IN most other surgical diseases, the results in the mortality rate following operation for goiter have improved considerably during the past one or two decades, but due to factors primarily not related to surgical technique. Surgical technique in thyroidectomy itself has changed or improved but little during the past three or four decades. However, numerous improvements in preoperative preparation (for example, use of thiouracil), choice of patients for operation, etc., have been made during this period. Most of these improvements are related directly to a better understanding and fuller appreciation of physiologic principles. Most of the physiologic principles are new. However, some are old and very obvious; it is amazing that so little attention has been paid to them during the years past.

PREOPERATIVE PREPARATION

Since the mortality rate of thyroidectomies in patients with mildly toxic goiter is very low indeed, the adherence to strict principles in preoperative treatment becomes much less important than it is in patients with severe toxicity. In other words, patients with mildly toxic goiter may require very little preoperative preparation. As will be discussed later, factors other than preoperative preparation must be considered seriously in patients with severely toxic goiter.

Administration of Iodine or Thiouracil.—Unquestionably, the administration of iodine or thiouracil in the preparation of patients for operation for toxic goiter is the greatest single factor in the maintenance of low mortality rate. The profession owes a debt of gratitude to Plummer for rediscovering the influence of iodine in toxic goiter and to Astwood for the clinical demonstration of the beneficial effects of thiouracil.

The dose of iodine usually given is from 5 to 15 minims three times daily, although a smaller dose is probably adequate. Doses larger than this are highly undesirable since nausea may be produced by an excessive dose of iodine. This would therefore defeat one of the primary purposes in the preparation of the patient, namely, to improve his nutrition. The greatest error in iodine therapy is continued use of the drug over a long period, that is, beyond preoperative preparation. The next greatest error lies in the assumption held by many physicians that

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maximum benefit of iodine therapy is attained between the tenth and fourteenth day. It is true that the average patient with thyrotoxicosis achieves sufficient beneficial effect at the end of fourteen days to be a perfectly safe operative risk. However, in patients who are extremely toxic, the optimum state of operability is practically never achieved within this period. In other words, the physician must maintain iodine therapy for many more days, realizing that improvement will still be achieved and that operations can be performed much more safely at a later date. The author admits the possibility of the patient becoming iodine-fast but wishes to emphasize that this danger is not as important as many clinicians would lead one to believe. It should be emphasized that these remarks on the use of iodine now apply only to those few patients who are sensitive to thiouracil or do not respond to it. However, some clinicians are using iodine and thiouracil together in preoperative preparation of the patient, giving thiouracil for a few weeks before iodine therapy is started.

The administration of thiouracil as introduced clinically by Astwood,[1] and discussed elsewhere in this symposium, may eliminate most of the worry on the part of the clinician in treating patients with a severe grade of toxicity. Although the effect of thiouracil requires a longer period of treatment than noted in iodine therapy, the decrease in toxicity is much more pronounced. In other words, the danger of a postoperative crisis and other complications arising from severe toxicity may be eliminated entirely with thiouracil. The fact that it requires a much longer time than iodine for its beneficial effect may prevent its routine adoption in patients with mildly toxic goiter. On the contrary, use of iodine in patients with severely toxic goiter may become obsolete except to supplement thiouracil. As discussed elsewhere in this symposium, continued use of thiouracil may result in permanent cure in many cases without the aid of operative therapy.

Increased Caloric Intake.—Although the factors in the pathogenesis of toxicity in patients with thyrotoxicosis are poorly understood, it is nevertheless surprising what little microscopic evidence of damage from excess production of thyroxin or allied compounds is found. It is, of course, well known that the increase in output of thyroid hormone (or abnormal chemical related to it) is largely responsible for the tachycardia and cardiac damage. Nevertheless, a great portion of the manifestations and pathologic changes are related to the negative caloric balance, largely secondary to the increased metabolism. It is, therefore, obvious that restoration of nutritional balance is exceedingly important, particularly in preparation of the patient for operation. The importance of this disturbance can be appreciated more readily when we realize how much greater than normal is the metabolic activity in toxic goiter. The increase in the metabolic rate may be sufficient to burn more than two or three times the amount of calories consumed by the average individual. It therefore becomes obvious that the cal-

oric intake must be increased accordingly before the patient can show an improvement in his nutritional status.

We place every patient with thyrotoxicosis of more than average degree on a diet of 5,000 calories per day. Men who are extremely toxic will frequently eat as much as 6,000 calories per day. As a matter of fact, caloric intake should be increased as long as the patient is capable of consuming additional food. Occasionally, in these severely toxic patients, administration of even this much food will not produce an appreciable gain in weight. Under such circumstances it may be wise to supplement the oral intake by intravenous glucose and amino acids (Elman[2]), at least over a period of a few days in order to achieve operability. The necessity of supplementing oral intake with intravenous solutions will be encountered most dramatically in the patients who are admitted in crisis or precrisis state. However, very frequently certain patients (particularly women) will have poor appetites, and be unable to eat a sufficient quantity of food even though they are not toxic enough to be classified as in a precrisis state.

Conservation of Energy.—Since a patient with toxic goiter is burning up food at a much greater rate than a normal individual, it becomes obvious that energy must be conserved at all possible points. Obviously the patient must be removed from manual labor or any activity which requires undue muscular exertion. However, he must not be confined to absolute bed rest since that produces a severe degree of muscle atrophy even within a short period of a few days. The patient should, therefore, be allowed to be up and about, so that he obtains sufficient exercise to prevent muscle atrophy. However, patients who are in a state of cardiac decompensation, and patients who are in crises or impending crises, represent exceptions and must be confined to absolute bed rest until these states are corrected.

Since sleep is so important in the conservation of energy, the patient must be urged to spend eight or nine hours in bed at night and take an afternoon nap two or three hours daily as part of the preoperative treatment. Since one of the manifestations of thyrotoxicosis is sleeplessness, the patient with severe toxicity will invariably need help in obtaining sufficient sleep. With few exceptions the routine administration of one of the less harmful sedatives, such as phenobarbital and allied compounds, will be indicated. It may be sufficient to limit the drug to a dose in the evening on retiring, although there is no objection to giving the drug two or three times daily to patients who are severely toxic.

Reduction of Psychic Trauma.—Unquestionably, excitement and worry increase the manifestations of thyrotoxicosis and therefore should be reduced to an absolute minimum, particularly if the patient is already toxic. Sources of excitement and worry are, of course, innumerable and include such factors as illness in the family, too much

social activity, financial difficulties, family incompatibility, and unruly children. Under such circumstances it will be necessary to remove the patient from family surroundings and take him to the hospital. Members of the family should be instructed not to inform the patient of family troubles or other difficulties which might increase worry. In the author's opinion, the severely toxic patient must be removed to a hospital for preoperative preparation, but the patient with mild toxicity should be ambulatory during preoperative care. In our clinic, at least three-fourths of the patients are prepared for operation in the outpatient department and are brought into the hospital two or three days before operation, for confirmation of operability.

Treatment of Complicating Diseases.—It is, of course, essential that the patient be examined thoroughly, so that no complicating diseases are overlooked. Diseases such as cardiac decompensation will, of course, be recognized at once since the major symptoms will be related to this condition. On the contrary, certain serious diseases, such as diabetes, may be discovered only upon thorough examination including laboratory work. Studies made by Regan and Wilder[3] revealed an incidence of diabetes in 1.7 per cent of patients with toxic diffuse goiter, which was identical to the incidence among all types of patients applying at the Mayo Clinic for medical care. However, in toxic nodular goiter the incidence of diabetes was much greater, being encountered in 5.6 per cent of the patients.

Hepatic insufficiency (as emphasized by McIver[4] and others) in a mild form is common; now and then it is the primary cause of a postoperative death. Such conditions must be recognized and treated before operation. Some of these conditions are entirely unrelated to the thyrotoxicosis whereas others are secondary to thyrotoxicosis. Details of the treatment of these conditions are discussed elsewhere in this symposium.

Miscellaneous Therapy.—In the author's opinion x-ray treatment may be very beneficial in the preoperative preparation in severely toxic patients, but is obviously indicated only in that small group of severely toxic patients who do not respond to thiouracil or iodine or both. There is no truth in the statements offered by some surgeons that x-ray treatment adds tremendously to operative difficulties. Very few, if any, adhesions are produced by x-ray therapy. It is true that the firmness of the gland may be increased but this will usually be an advantage to the surgeon since friability frequently leads to an increase in hemorrhage incident to the operation. True enough, the maximum effect of x-ray therapy may not be attained in less than four to six weeks. However, except during the two or three days following treatment itself, there should be no deleterious effects from radiation of the gland.

As an example of the value and danger of x-ray therapy, I would like to summarize briefly our experience (before thiouracil was available) with one of the most toxic patients we have had. This individual, a woman

about 30 years of age, entered the hospital in a precrisis state and after weeks of intensive therapy was still obviously inoperable. X-ray therapy was decided upon and was instituted. A day or two following radiation, which was given over a period of a few days, she developed a severe increase in symptoms and was in a state of mild crisis. During this period she became jaundiced, indicating an increase in hepatic insufficiency. For a time it appeared that the institution of radiation may have been an error. However, during the course of the next few weeks she showed gradual improvement and for the first time since admission, many weeks previously, began to show a gain in weight. For the five weeks following radiation she improved to such an extent that she was considered operable according to the prerequisites described later. The patient was submitted to operation, consisting of removal of only one lobe. This was tolerated well and the second lobe was removed three or four weeks later.

Curtis and associates[5] have demonstrated a negative calcium balance in hyperthyroidism, thereby illustrating the need for calcium therapy. In addition, it is agreed that certain vitamins, particularly B_1, are utilized in a more rapid rate in thyrotoxicosis. Administration of additional vitamin B_1, therefore, is indicated.

Although every surgeon probably has a scheme of his own for determining operability, everyone will probably agree that the methods of determination of operability are quite arbitrary and therefore subject to many errors. The lack of specificity in outlining methods of determining operability is brought to light more emphatically when one tries to explain to students how a decision regarding operability is arrived at. Under the circumstances it is obvious that if a system utilizing mathematical relationships could be adopted in this determination of operability, the method would be more accurately utilizable by everyone, particularly the students.

PREREQUISITES FOR BILATERAL THYROIDECTOMY

It is because of the difficulty in explaining verbally the various physical characteristics required that we have adopted the following group of prerequisites for determining operability. In other words, we require that the patient fit the prerequisites as listed, before he is acceptable for a bilateral thyroidectomy. As will be discussed later, if the patient's condition does not meet the requirements listed here, even after many weeks of therapy, the operation should be done in two stages, removing one lobe at each operation. If the patient's condition fails by a wide margin to meet prerequisites, even lobectomy may be unsafe. As stated previously, the use of thiouracil will eliminate most of this difficulty by eliminating the severe toxicity. However, the occasional instance of sensitivity, or failure of response to the drug, will make it necessary that we retain our knowledge of determination of operability in the presence of severe toxicity.

1. *Gain in Weight.*—Without question the most important requisite for operability in the really toxic patient is gain in weight. *At no time should the severely toxic patient be submitted to thyroidectomy when he has failed to show a weight gain.* As already stated, it is important to start the severely toxic patient on a caloric intake equal to, or more than, 5,000 calories per day. It is not enough to tell the patient to "eat a lot" since that is not sufficiently specific. If he is severely toxic he should be prepared in the hospital for operation. It is difficult in the home to be certain that the patient is getting the 5,000 or 6,000 calorie diet necessary for him. There is no rule as to the exact amount of weight gain necessary. However, certain general premises can be established. For example, if the patient has lost thirty or forty pounds and is obviously malnourished, he will need to gain at least ten to twenty pounds before his physical condition is optimum. On the contrary, if he has lost only eight or ten pounds, a gain of two to four pounds may be adequate to assure the added caloric requirements with replenishment of the various food depots.

Gain in strength is allied to a gain in weight and should be considered in the prerequisites. Numerous methods of determining gain in strength are utilized by various clinicians. For example, some surgeons feel that a patient should be strong enough to walk up a certain number of stairs before operation is considered safe. Others say that he should be able to walk from one to two blocks without undue fatigue. Still others have less strenuous muscular feats, such as stepping up on a chair, or lifting weights, as prerequisites. The patient's ability to hold his breath has been suggested as a mechanism for determining operability.

2. *Resting Pulse Rate Should Be Below 110.*—Except in the presence of severe cardiac damage, particularly auricular fibrillation, the pulse rate will be a fairly good index of toxicity. Obviously, the pulse rate will vary throughout the day, depending upon exercise, excitement, etc. We have adopted the principle that the resting pulse rate should be below 110. If a tachycardia of 130 or above develops with only slight excitement or exercise, it is considered that the patient's toxicity is greater, and the cardiac reserve lower than other signs may indicate.

3. *Basal Metabolic Rate Should Be Less Than 50 Per Cent Above Normal.*—Although we appreciate the fact that the basal metabolic rate is subject to considerable error in determining the patient's toxicity, we have nevertheless found it of value when this information is added to the other available data. With few exceptions any patient with a basal metabolic rate of over 50 (after iodine or thiouracil therapy) is apt to have considerable reaction following an operation. The metabolic rate before iodine therapy is of little consequence in determining the operability.

4. *Response to Iodine or Thiouracil Therapy.*—Very rarely indeed will a toxic patient fail to improve markedly under iodine therapy. There should be a definite decrease in intensity of most of the symptoms such as nervousness, excess sweating, sleeplessness, and weakness. Inclusion of this prerequisite is perhaps of more value in establishing the diagnosis in doubtful cases than it is in determining operability, largely because the other prerequisites mentioned are dependent upon a response to iodine or thiouracil.

5. *No Untreated Complications.*—The necessity of effectively treating cardiac decompensation, which is usually secondary to the thyrotoxicosis, is well known and is discussed elsewhere in this symposium. The vital capacity should always be determined in patients with cardiac complications; a figure significantly below normal would suggest that the decompensation was as yet inadequately treated. It must be emphasized that numerous complications unrelated to the thyroid disease may be present. Diabetes, local infections, etc., are representative of unrelated disease which must be treated adequately before operation can be considered.

FACTORS RESPONSIBLE FOR INCREASED MORTALITY RATE

Before discussing the numerous factors which might be responsible for an increase in mortality rate, I would like to discuss the various causes of death in our series following thyroidectomy, and indicate the types of goiter in which such disasters might be expected. Obviously, before the time of iodine or thiouracil therapy, development of crisis was the most common cause of postoperative death. Since the use of these drugs, crisis is becoming rare as the cause of death. In fact it might be said that death from crisis following thyroidectomy is inexcusable, and in reality can be prevented with practically no exceptions.

In Table I, it will be noted that in a total of 936 thyroidectomies for toxic diffuse goiter, toxic nodular goiter, and nontoxic nodular goiter, the overall mortality rate was 1.06 per cent. This does not compare too favorably with a rate of 0.76 per cent in 19,700 thyroid operations reported by Lahey.[6] However, it should be added that the rate reported by Lahey represents about the lowest record for a large series. In Table I it will likewise be noted that the mortality rate in the patients with toxic diffuse goiter is lower than in patients with nontoxic nod-

TABLE I

TYPES OF GOITER AND MORTALITY, 1936 TO 1944
(Excluding Carcinoma and Woody Thyroiditis)

TYPE	OPERATIONS	DEATHS	MORTALITY (PER CENT)	
Toxic diffuse	403	3	0.74	1.14
Toxic nodular	297	5	1.6	
Nontoxic nodular	236	2	0.85	
Total	936	10	1.06	

ular goiter. This in reality is not surprising, since we realize that patients having toxic diffuse goiter are relatively young and that preparation is usually carefully carried out before operation is performed. On the contrary, our patients with nontoxic nodular goiter are much older than those with toxic diffuse goiter; even though they are not affected with thyrotoxicosis, they still are subject to serious organic disease, particularly that related to the heart.

Table II reveals that the two deaths encountered in nontoxic nodular goiter were caused by acute heart failure. With the exception of acute heart failure, there is surprisingly little duplication of causes of death in the entire list. For example, the five patients who died following thyroidectomy for toxic nodular goiter, died of a different complication, namely, crisis, hemorrhage, gas gangrene of the buttocks, acute heart failure, and severe glucose reaction.

It is true that the patient listed as having died following the severe glucose reaction might have survived if she had not had a toxic goiter, yet from the clinical findings, there is sufficient reason to believe that she would have survived quite satisfactorily if the severe glucose reaction had not developed. In other words, some of the causes listed are in reality contributory, but are considered to be the most important cause of death. In the entire group of ten deaths, it is obvious that at least four should be classified as preventable, namely, those due to hemorrhage, crisis, and glucose reaction. We, therefore, accept full responsibility for these fatalities, and in retrospect feel that we should have prevented them.

TABLE II

CAUSES OF DEATH FOLLOWING THYROIDECTOMY

Toxic diffuse	3	1 Tetany 1 Crisis 1 Acute hepatic insufficiency
Toxic nodular	5	1 Crisis 1 Hemorrhage 1 Gas gangrene of buttock 1 Acute heart failure 1 Severe glucose reaction
Nontoxic nodular	2	2 Acute heart failure

It is obvious then from the variety of the causes of death shown in our series, that lowering the mortality rate may be difficult, except in the instances such as the four just mentioned. In spite of the great variety of causes of death, the author is convinced that if the mortality rate following operation is much above 1 per cent, insufficient attention is being paid to certain prerequisites, or postoperative care is not what it should be.

Although in a consideration of mortality rates throughout the country the relative incidence of the types of goiter encountered might be

considered as playing a prominent role in the fatalities, I doubt that this factor plays a significant role. The patients in the series herein reported came from Chicago or environs, which is in the center of one of the most prominent goiter belts in the United States. Yet the ratio of toxic diffuse to toxic nodular and nontoxic nodular goiter is almost identical to the ratio reported by Lahey[6] as being encountered in Boston, namely, 2 to 1 to 1, respectively. In our experience, thyroidectomy in patients with toxic nodular goiter is associated with a much higher mortality rate than in toxic diffuse goiter (see Table I). Our death rate was more than twice as high in toxic nodular goiter as in toxic diffuse goiter. I believe that this trend would be maintained in almost all localities although there might be an exception in a series composed largely of private patients, since this group of patients with toxic nodular goiter would be much less likely to postpone treatment of the insidious manifestations so typical of this type of goiter; the symptoms of toxic diffuse goiter are so prominent that charity and private patient alike will come early for treatment before serious organic changes take place.

1. *Inadequate Preparation.*—Unquestionably the most common factor in inadequate preparation is failure on the part of the physician to supply enough food to produce a gain in weight and put the patient on a positive caloric balance.

2. *Wrong Choice of Time for Operation.*—It is well known that the degree of toxicity fluctuates considerably in patients with toxic goiter. Therefore, in the treatment of severely toxic patients it is usually necessary to choose a time for operation when the patient is in a so-called remission. During this time his manifestations may fit into the prerequisites previously outlined although it may require several weeks of therapy before this state of operability can be achieved. It should be remembered that certain features in the daily life of the patient may actually alter the operability. For example, if a patient is confronted with the news of the death of a member of his family, he may immediately revert from a state of operability to one of inoperability, and require several days of therapy before operability is regained.

3. *Lack of Appreciation of the Danger of Complications.*—It need not be emphasized that a patient who has a complication along with hyperthyroidism will, of course, not be as good a risk as a patient without complications. The report of Pemberton and Miller,[7] who note that 81 per cent of their deaths were in thyrocardiac patients, illustrates this point very emphatically. It is obvious that in the group of patients with complications the prerequisites outlined must be met more completely than in other patients.

4. *Errors on the Operating Table.*—Failure to recognize signs of excessive toxicity is probably the most common error made while the

patient is on the operating table. Ordinarily the surgeon has ample warning at this time of the presence of severe toxicity. In the first place, the pulse rate during the anesthesia is an important indication of toxicity. We utilize the principle that if the pulse rate cannot be brought down under 140 with anesthesia, operation is so unsafe that the incision should not even be made; under such circumstances it is advisable to send the patient back for a few more days of treatment. Likewise, if after the removal of one lobe, the patient's pulse starts to rise above 135 or 140, it is usually wise to terminate the operation at this point. The use of an excessive amount of oxygen is likewise an indication of toxicity. If the anesthetist informs the surgeon that it is extremely difficult to keep the patient oxygenated under general anesthesia, it is safe to assume that the patient is probably more toxic than was originally considered. Utilizing the principle just discussed, we have sent many patients back from the operating room before making the incision, and in about 5 per cent of the cases we do the operation in stages, removing the right lobe at the first operation and the left lobe from three to six weeks later. Too frequently the surgeon inflicts too great an operative load upon the patient. The author agrees wholeheartedly with Lahey,[6] who states that many of the deaths encountered are explained on the basis that two much work has been done, namely, that two lobes were removed instead of one. It should be emphasized that if before operation the surgeon has arrived at the decision to do the operation in two stages, rarely is it safe to allow a smooth course on the operating table to change his decision to that of removal of both lobes.

Errors in technique are of less importance in the mortality rate than are errors in judgment. However, if a bilateral recurrent nerve injury is sustained in a severely toxic patient, the excess load of anoxia, tracheotomy, etc., may be sufficient to cause death. On certain occasions, slowness in performance of the operation may be a most important contributory factor in the patient's death. This would be true only in the patient who is severely toxic. Although the author agrees that thyroidectomy should be done with the utmost dispatch in severely toxic patients, he would like to emphasize that efforts to hurry and shorten the operating time have probably done more harm than good, except in emergency circumstances. In general, if a high mortality rate is secondary to inexperience on the part of the surgeon, failure to utilize proper judgment in preoperative care, choosing the proper time for operation, etc., will reflect much more directly on mortality rate than will poor operative technique.

The choice of anesthesia may likewise reflect somewhat in the mortality rate. Perhaps the best example of this might be the use of cyclopropane in a patient with auricular fibrillation who has considerable myocardial damage. Likewise the use of nitrous oxide in the

hands of a poor anesthetist might be dangerous in severely toxic patients, although we realize that experts can handle this agent very well.

5. *Insufficient Vigil in Postoperative Care.*—Perhaps the most common example of fatality resulting from failure to exercise proper postoperative care is failure to recognize and promptly treat postoperative hemorrhage and bilateral injury to the recurrent nerve. Insufficient fluid, too little or too much sedation, failure to utilize oxygen therapy when indicated, and numerous other errors may contribute to a postoperative fatality. Details of these features in postoperative care are discussed at length, elsewhere in this symposium.

SUMMARY

The marked improvement in mortality rate following thyroidectomy during the past one or two decades has been due primarily to improvements in our knowledge and application of physiologic principles, particularly as related to preoperative and postoperative care. Preoperative preparation is exceedingly important in patients with severely toxic goiter. The major factors in this preparation of the patient include: (1) administration of iodine or thiouracil; (2) increased caloric intake; (3) conservation of energy; (4) reduction of psychic trauma; (5) treatment of complicating disease; and (6) miscellaneous therapy. Appreciating that the mortality rate is so dependent upon preoperative treatment, we have adopted in our clinic certain prerequisites to be met before a patient is considered safe for bilateral thyroidectomy. These prerequisites are: (1) gain in weight; (2) resting pulse rate below 110; (3) basal metabolic rate below 50; (4) response to iodine or thiouracil; (5) no untreated complications. Of this group of prerequisites, gain in weight is the most important. It is an unforgivable error to subject a patient with severe toxic goiter to bilateral thyroidectomy, unless he has shown a weight gain.

Thiouracil gives promise of revolutionizing our methods of preoperative care and may make operation unnecessary in many patients. However, it is doubtful if the mortality rate may be appreciably lowered in the clinics reporting the best results, largely because relatively few of the deaths encountered in such series of patients will be related to thyrotoxicosis itself. The mortality rate in our series of 936 thyroidectomies was 1.06 per cent. It was lower in toxic diffuse goiter than in either of the two types of nodular goiter. Although almost one-half of our deaths must be considered in the preventable class, the causes were extremely variable. Three patients died of acute heart failure, and two died in crisis. There was no duplication in the other causes of death. A study of factors (other than coincidence) which might be responsible for a lethal outcome includes: (1) inadequate preparation; (2) wrong choice of time for operation; (3) lack of appreciation of the dangers of complications; (4) errors on the operating table; (5) insufficient vigil in the postoperative care.

It should be emphasized again that many of the precautions described here will be of only slight importance in the great majority of patients who respond to thiouracil. However, since an occasional patient will be sensitive to the drug or will not respond to it, information gained about severely toxic patients through many years' experience with them should not be cast aside.

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ANESTHESIA IN THYROID SURGERY

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METHODS of anesthesia for operations on the thyroid gland are many and diversified and the approach to the anesthetic problems involved in this type of surgery is governed somewhat by the conditions under which the surgeon likes to work. Of the available methods from which to choose, most provide satisfactory working conditions for the surgeon and an adequate margin of safety for the patient.

Surgeons performing thyroid operations may be divided roughly into two groups from the standpoint of their choice of anesthesia. Surgeons of one group prefer that their patient be asleep throughout the course of the operation and hence favor inhalation or intravenous anesthesia. Those of the other group favor having the patient awake, at least intermittently, throughout the operation in order that his speaking voice may be checked at intervals for possible damage to the recurrent laryngeal nerve and to permit straining in order that all potential bleeding vessels may be ligated securely before the wound is closed. This group prefers local or regional anesthesia with only the intermittent use of a general anesthetic agent.

Thyroid surgery presents certain anesthetic problems related both to the nature of the disease and to the site of the operation that are not encountered in most other types of surgery. Despite the fact that a surgeon may prefer a certain type of anesthesia in uncomplicated cases, some conditions make certain types of anesthesia preferable to others. Such conditions might include very large glands; substernal goiters; those which are causing undue pressure on, or displacement of, the trachea; dyspnea; cardiac disease; and severe thyrotoxicosis. In this type of case the anesthetic management is of greater importance than for an operation for a simple nontoxic adenomatous goiter.

Some features of the anesthetic management of thyroid patients bear particular attention. The fact that many patients suffering from goiter have varying degrees of elevation of emotional tone necessitates individualized adjustment of the preliminary medication to effect adequate preanesthetic sedation. Since the site of the operation is in close proximity to the trachea and upper respiratory passages, respiratory obstruction is always a potential hazard. Because of the elevation of the metabolic rate, anoxemia is not only undesirable but even dangerous, since these patients have a high oxygen requirement.

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Respiratory obstruction, in addition to inhibition of oxygenation, complicates the surgical procedure by increasing bleeding in the operative field. These are some of the considerations that must be weighed in selecting the anesthetic agent for the patient suffering from a disease of the thyroid.

PRELIMINARY MEDICATION

Patients who have a disease of the thyroid, particularly those who have severe hyperthyroidism, require adequate preliminary sedation in order to lower their emotional tone to somewhere near basal level. Various premedicants and basal sedatives have been employed for this purpose. Avertin with amylene hydrate has attained favor with many surgeons for the production of basal anesthesia in operations on the thyroid. We prefer the use of morphine and a barbiturate in divided doses since this method appears to have greater flexibility than the single administration of basal sedatives by rectum. Pentobarbital sodium is administered the night before operation in doses of 1½ to 3 gr. (0.1 to 0.2 Gm.). The dose should be sufficient to insure a good night's rest. On the morning of the operation the dose or doses of pentobarbital sodium are repeated and ⅙ gr. (0.01 Gm.) of morphine and $\frac{1}{150}$ gr. (0.00043 Gm.) of atrophine are administered hypodermically at least one-half hour before the time of operation. The important feature is to adjust the dosage and timing of the premedicants so that the patient reaches the operating room in a drowsy and peaceful state of mind. Some physicians prefer to have the patient asleep before leaving his room.

In spite of a carefully planned course of preliminary medication, such things as unforeseen delays result in many patients reaching the operating room inadequately premedicated. When this occurs, additional doses of pentobarbital sodium may be administered intravenously after the patient reaches the operating room. The drug, in 2.5 per cent solution, is injected slowly and intermittently until the basic level of sedation is reached. This should render the patient drowsy but not asleep. If the thyroid condition has resulted in any degree of respiratory obstruction, only minimal sedation is indicated in order to avoid respiratory depression, obstruction, and anoxemia.

Much stress has been placed on the preoperative management of the patient suffering from disease of the thyroid in regard to absolute rest and quiet and shielding him from the knowledge of anything relative to the operation or its time. No doubt such measures are justified in the management of patients who are extremely hyperactive but for the average patient we feel that these precautions are unnecessary, provided the course of preliminary medication is adequate. Most of these patients get along well on ordinary routine preoperative management and it often seems that special attentions render them more, instead of less, apprehensive.

ANESTHETIC AGENTS AND METHODS

When the thyroid condition has resulted in severe metabolic imbalance and hyperfunction, anesthetic agents having the least toxicity and which interfere least with metabolic function are indicated.

Local and Regional Anesthesia.—Provided the patient has been well premedicated, local anesthesia has many advantages. It is adequate for most stages of the operation and produces the minimum of secondary toxic effects. Our method consists in blocking the superficial cervical plexus bilaterally with 1 per cent solution of procaine hydrochloride or metycaine and infiltrating the region of incision with a 0.5 per cent solution of one of these drugs. The use of epinephrine as a vasoconstrictor in the local anesthetic solution is contraindicated if the gland is of the toxic or exophthalmic type. It is to be remembered that some patients are definitely sensitive to epinephrine and many so-called procaine reactions have been due to this vasoconstrictor. In cases of nontoxic thyroid conditions, cobefrin may be used as a vasoconstrictor. Usually, sufficient duration of anesthesia is obtained without a vasoconstrictor, particularly if metycaine is used. Most of the discomfort under local anesthesia occurs when the lobes are being delivered and when traction is made on the gland. Brief periods of supplementation with nitrous oxide and oxygen at these times render the patient comfortable. The local anesthesia permits the use of sufficient oxygen with the nitrous oxide to prevent most patients from becoming cyanotic. This combination of methods makes it possible to have the patient awake whenever necessary. The advantages of this have been mentioned heretofore.

Block Anesthesia.—In certain cases in which the patient is an extremely poor risk, because of debility, toxicity, or the size and position of the gland, it may be undesirable to put the patient to sleep. In such cases complete cervical block will provide anesthesia of all the deep and superficial structures. This is accomplished by bilateral injection of 1 per cent solution of procaine or metycaine into the second, third, and fourth cervical nerves and the superficial cervical plexus. The region of operation is also infiltrated with a 0.5 per cent solution of one of the agents.

Inhalation and Intratracheal Anesthesia.—Nitrous oxide, ethylene, and cyclopropane have all been employed in thyroid surgery and, because of their inert nature, are suitable agents. However, nitrous oxide-oxygen anesthesia alone often fails to provide sufficient depth of anesthesia without the patient becoming cyanotic, which is to be avoided. To a lesser degree this also applies to ethylene. The value of these agents in thyroid surgery is enhanced if they are complemented by local or regional anesthesia.

Cyclopropane is considered by many to be the agent of choice if inhalation anesthesia is to be used. It produces quiet breathing, while

anesthesia can be maintained with a comparatively high concentration of oxygen. These features together with the rapid recovery period commend its use in operations on goiter. The main drawback of cyclopropane is its explosibility but this need not necessarily contraindicate its use if proper precautions are observed. With the proximity of the field of operation to the upper respiratory passages, the employment of electrical apparatus during the operation would, we feel, contraindicate its use.

Most surgeons and anesthetists agree that as a rule ether is not a desirable agent for routine use in operations on the thyroid. However, if it is felt that an inhalation anesthetic agent is indicated (perhaps with an intratracheal tube) moderate amounts of ether may be administered with comparative safety to a patient for whom a gaseous anesthetic agent is inadequate. For a child undergoing an operation on the thyroid, inhalation anesthesia, preferably intratracheal, becomes the method of choice and moderate amounts of ether may be administered without untoward effect.

If an inhalation anesthetic agent is preferred by a surgeon, the operation may be performed with greater facility if an intratracheal tube is used. Its use will permit a continuously free airway, regardless of the position of the patient's head or pressure or traction exerted on the larynx and trachea. In addition, adequate ventilation and oxygenation may be maintained. Intratracheal anesthesia is probably the method resulting in the most efficient second-to-second control if the gland is large or substernal or if there is pressure on, or deviation of, the trachea. It is good prophylaxis to have an intratracheal tray in readiness, with several sizes of intratracheal tubes and a laryngoscope, whenever an operation on the thyroid is being done, regardless of the type of anesthesia employed. This prevents delay in establishing the airway, the need for which may occur suddenly in occasional cases.

Intravenous Anesthesia.—During the past ten years the use of intravenous pentothal sodium anesthesia has been increasing for all types of surgery. Many thyroid surgeons favor its use in this field. From certain standpoints it is suitable, since it does not untowardly affect the metabolic processes of patients suffering from thyroid disease. The comparative freedom from nausea and vomiting following pentothal sodium anesthesia is desirable and it may be used with any amount of oxygen the patient may require. On the other hand, certain technical factors may enter the picture. If pentothal sodium is used as the sole anesthetic agent, mechanical obstruction of the upper part of the respiratory tract or obstruction due to laryngeal spasm can occur. Since the laryngeal reflexes probably will be still active, it may be difficult to insert an intratracheal tube without trauma, if the need arises. Certain patients suffering from thyroid disease who are unusually hyperactive may require large amounts of the drug, which may result in a prolonged post-

operative sleep, accompanied by restlessness or excitation during recovery. All these side effects are undesirable.

For those who wish to take advantage of the desirable features of intravenous anesthesia, we feel that its use as an adjunct to other methods of anesthesia produces the best results. There are a number of possibilities that may be worthy of consideration. Pentothal sodium anesthesia provides a rapid and pleasant induction to inhalation anesthesia for patients who are upset and nervous. For certain patients this is carried out in their own room before they are taken to the operating room. If pentothal sodium is used as a supplement to local or regional anesthesia only minimal amounts of the intravenous agent may be required and it may be possible to arouse the patient at the end of the operation. When this method is used alone or as a supplement to other methods, oxygen or a mixture of 50 per cent nitrous oxide and 50 per cent oxygen should be administered during the course of the intravenous anesthesia. Combinations of pentothal sodium and the gaseous anesthetic agents may often prove useful when the use of ether is inadvisable. When the upper portion of a patient's respiratory tract becomes partially obstructed, helium-oxygen mixtures can be utilized to facilitate oxygenation of the patient.

COMMENT

Modern anesthetic agents and methods have been important in improving the preoperative, operative, and postoperative management of patients undergoing operations on the thyroid. The choice of anesthesia for these patients has been broadened in recent years so that there are many different anesthetic approaches to the various problems presented by the patient suffering from goiter. In order to obtain the fullest benefit from the choice of anesthesia, the problems of the individual case should be weighed preoperatively by the surgeon and the anesthetist. By such collaboration the surgeon can supply the anesthetist with information relative to the surgical requirements and possible complications. In this way, methods of anesthesia may be chosen which offer the patient the minimum of toxic effects from the anesthetic agent and which, at the same time, provide continuous control of the patient and of the complicating factors which may arise.

TECHNIQUE OF THYROIDECTOMY

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THE technique of subtotal thyroidectomy for exophthalmic goiter and toxic adenoma, as well as that of removal of a discrete adenoma, intrathoracic goiter, and the isthmus for constricting thyroiditis, is best demonstrated, I believe, by illustrations. Any technical procedure, such as a surgical operation, can be understood more adequately and more quickly, with less likelihood of misunderstanding, if it can be visualized. Since the accompanying drawings with their descriptive legends clearly show the various steps of the procedures, a lengthy discussion will be unnecessary.

The methods here presented are based upon the removal of over 23,000 goiters. These technical procedures are the result of progressive refinement of our technique prompted by added experiences and constantly widening contacts with all aspects of thyroid disease. While many of the fundamental steps were designed by me, some have been modified by other members of the Department of Surgery of the Lahey Clinic. These procedures, which are standard in this institution, have stood the test of time, numbers, and repeated follow-up studies.

COMMENT

While this presentation deals solely with surgical technique, I cannot conclude it without calling attention to the fact that the operative procedure is but one of several factors concerned in a successful thyroidectomy. Experienced judgment in the preparation of these patients and the decision concerning the optimal time for operation are of equal, if not greater, importance than the technical procedure. The same may be said of anesthesia and postoperative management, since without experience and judgment in these fields, a thyroidectomy, although scientifically executed, may have an unsatisfactory result. In no other field of surgery is a greater variety of skill and experience needed to obtain a good result and a low mortality. Here the knowledge of the cardiologist, endocrinologist, internist, anesthetist, and surgeon may be most advantageously combined in obtaining a satisfactory postoperative result.

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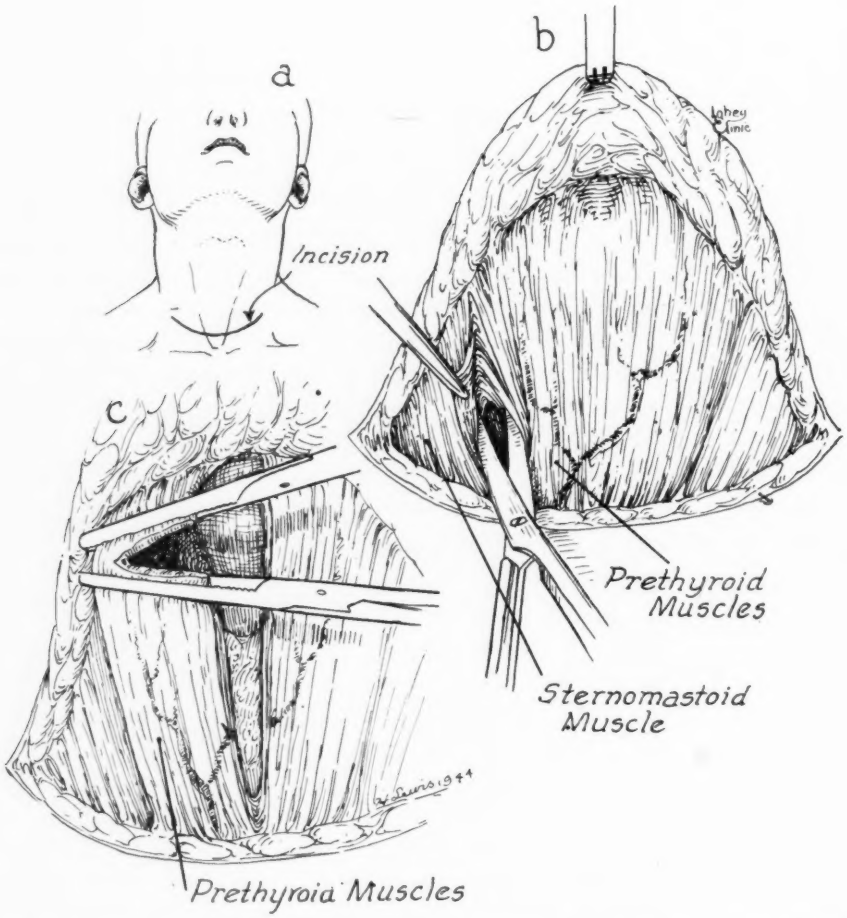

Fig. 1.—*a*, The curve employed in goiter incisions in this Clinic. With the chin elevated, the chest thrown forward, and the neck in the forward goiter position, the incision is placed a little higher than ultimately desired. When the chin comes down and the chest is lowered, the incision descends about 1 inch.

b, The height to which the skin flap is elevated. Good exposure of the thyroid gland requires elevation of the skin flap up to and above the level of the notch in the thyroid cartilage. This permits adequate exposure of the superior thyroid artery and veins at the upper pole of the thyroid gland where they enter, so that they may be ligated well off the thyroid gland. The sternomastoid muscle is being separated from the prethyroid muscle. The former will then be retracted so that when the clamps are applied across the prethyroid muscles, as in *c*, they can be clamped well out and wider exposure obtained.

c, The high level at which the prethyroid muscles are cut. The innervation remains undisturbed. The suture level will be well up under the skin flap where it will not interfere with closure of the skin incision or complicate its healing. A thyroidectomy can be done more safely and with better exposure if the prethyroid muscles are cut. Although thousands of prethyroid muscles have been cut and sutured at the Lahey Clinic, no deformity, disfigurement, or dysfunction has resulted.

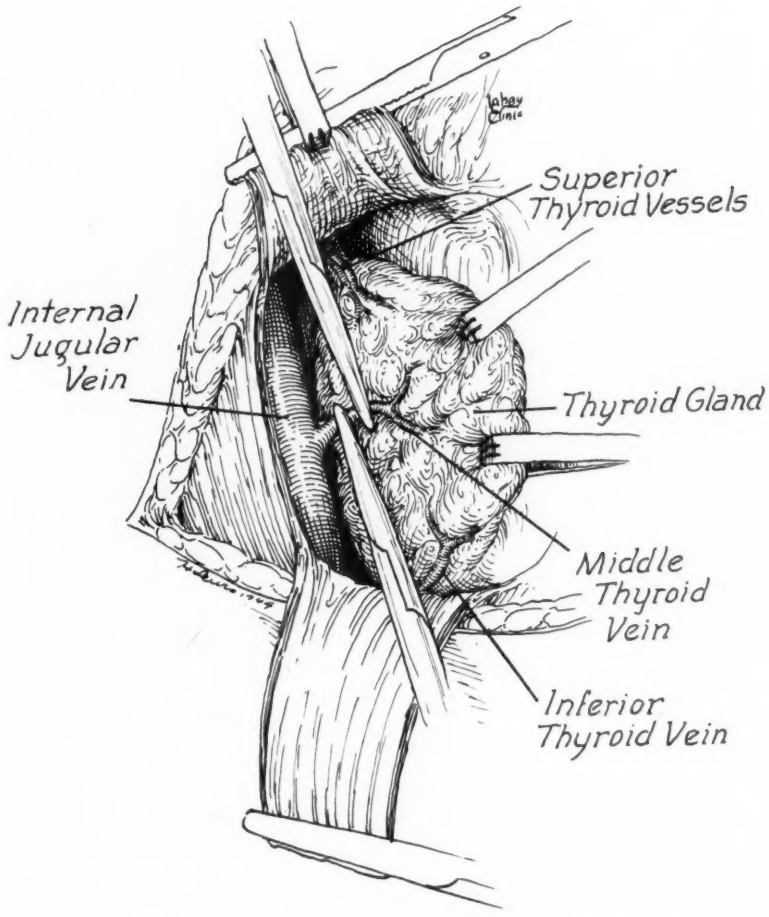

Fig. 2.—The internal jugular vein, and the middle thyroid vein as it enters the middle of the thyroid gland. The first step after exposure of the thyroid gland is severing the middle and inferior thyroid veins, which facilitates mobilization of the thyroid gland up out of its bed. Note the excellent visualization of the superior thyroid vessels when the skin and muscle flaps are elevated adequately. The double hooks, specially modified in this Clinic, lift the gland up out of its bed in order to obtain adequate exposure.

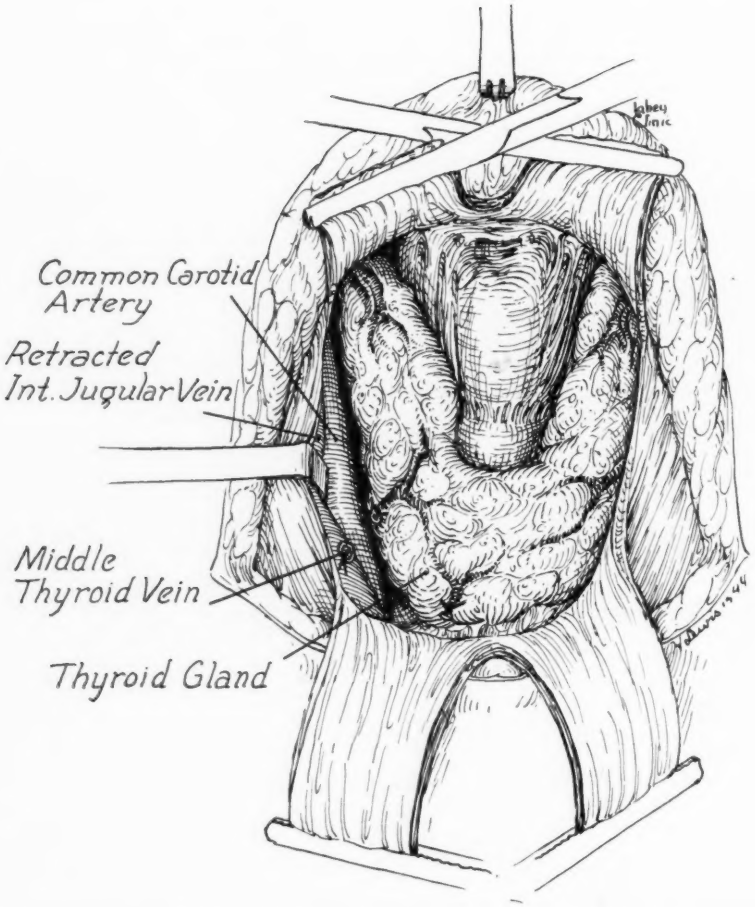

Fig. 3.—After the middle and inferior thyroid veins are ligated and severed, the internal jugular vein is retracted, thus exposing the common carotid artery, beneath which, with the gland lifted out of its bed, the inferior thyroid artery can be demonstrated. As a result of elevation of the prethyroid muscles above the level of the notch of the thyroid cartilage, the upper pole of the gland with its entering vessels is clearly exposed.

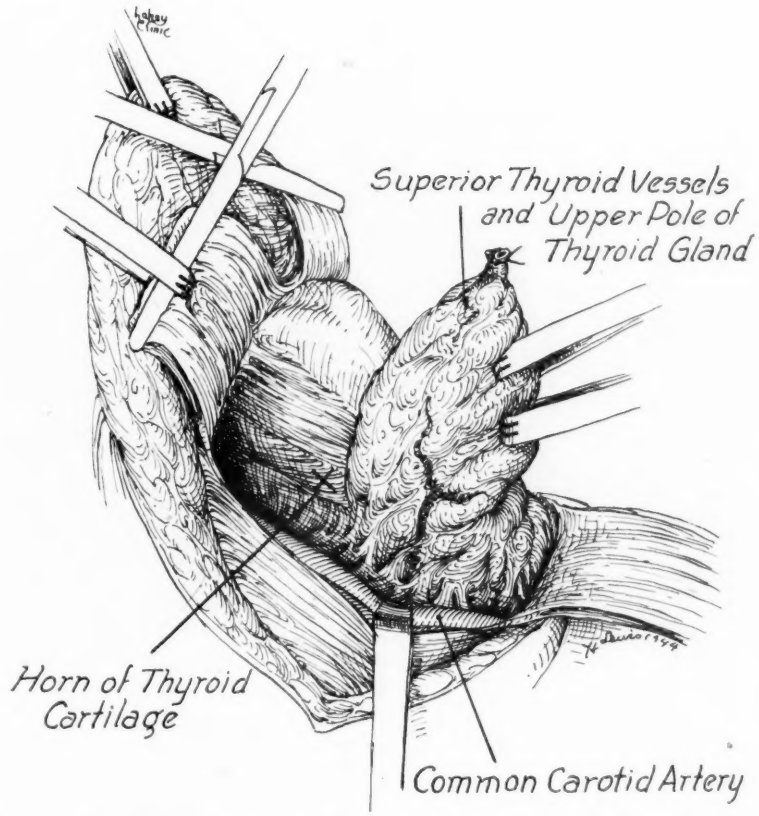
Lahey Clinic
Superior Thyroid Vessels and Upper Pole of Thyroid Gland
Horn of Thyroid Cartilage
Common Carotid Artery

Fig. 4.—The upper pole of the thyroid gland is mobilized after ligature of the superior thyroid vessels. The attachment of the thyroid lobe to the larynx has been freed, thus making possible a more radical removal of thyroid tissue (Fig. 5). Note the level of the horn of the thyroid cartilage. At this point the recurrent laryngeal nerve becomes intralaryngeal, so that above this there is no danger of injury. Note the retraction of the common carotid artery by means of which the inferior thyroid artery can be found and ligated.

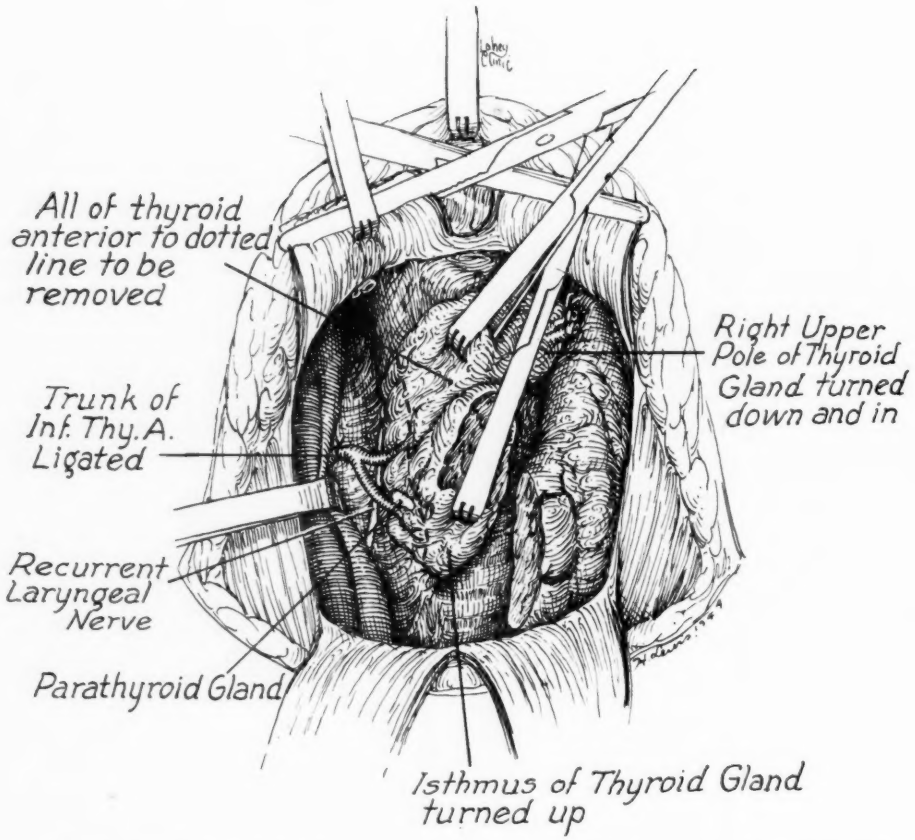
All of thyroid anterior to dotted line to be removed
Right Upper Pole of Thyroid Gland turned down and in
Trunk of Inf. Thy. A. Ligated
Recurrent Laryngeal Nerve
Parathyroid Gland
Isthmus of Thyroid Gland turned up

Fig. 5.—The internal jugular vein and common carotid artery have been retracted. The inferior thyroid artery has been demonstrated and ligated. The isthmus of the thyroid gland has been severed from the opposite lobe, separated from the trachea, and elevated upward. Note the usual location of the inferior parathyroid gland between the branches of the inferior thyroid artery. The thyroid tissue anterior to the dotted line is to be removed, and that behind it is the stump of thyroid gland to be left. A radical removal of the thyroid gland is made possible by freeing the upper pole and pulling it downward and freeing the isthmus and pulling it upward. The recurrent laryngeal nerve may be seen after visualization of the inferior thyroid artery.

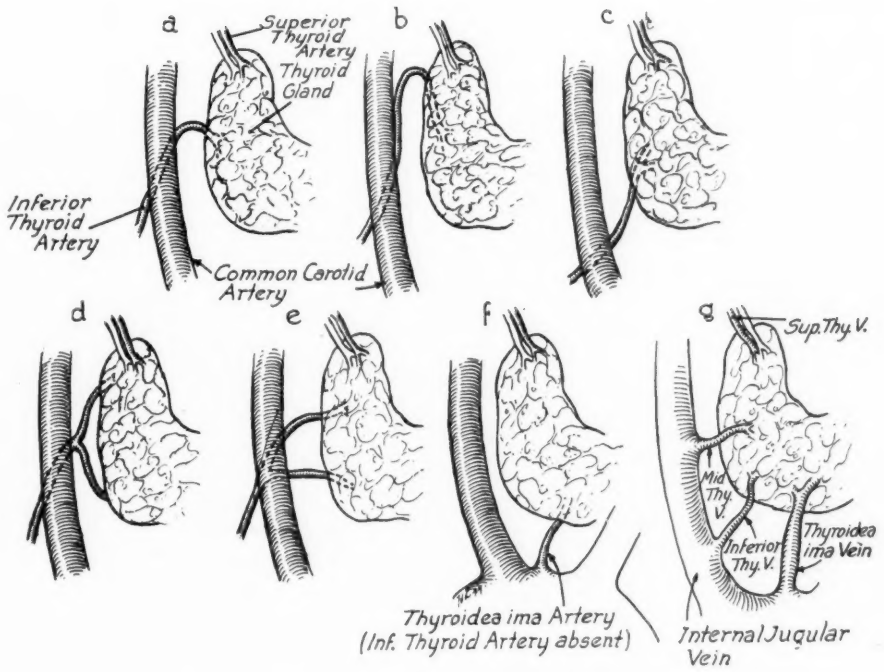

Fig. 6.—The various types and positions of the inferior thyroid artery.

a, A common type of inferior thyroid artery enters directly into the gland.

b, The inferior thyroid artery arches upward and sometimes descends behind the thyroid gland to enter it, the arch sometimes being as high as the superior pole.

c, The inferior thyroid artery which extends from below upward is the type most difficult to demonstrate. The surgeon is apt to think that the artery is absent because it is not in the most common positions (*a*, *b*, *d*, and *e*). Demonstration of this type of inferior thyroid artery requires elevation of the lower pole of the thyroid gland well out of its bed, retraction of the common carotid artery at a low point, and careful dissection of the deep cellular tissue under good light.

d, A common type of inferior thyroid artery, which divides well out from the gland.

e, The same type as *d*, with division of the inferior thyroid artery well behind the common carotid artery. Either the upper or the lower branch only may be demonstrated and ligated, and the second branch may be overlooked. This results in continued bleeding in the gland, which is not controlled or explained until the second branch is found and ligated.

f, The inferior thyroid artery is absent, the blood supply coming from a thyroidea ima.

g, The common location of the thyroid veins (middle, inferior, and ima). Complete mobilization of the thyroid gland and turning it up out of its bed (Fig. 5) require that all venous attachments between the thyroid gland and the internal jugular vein be ligated and severed.

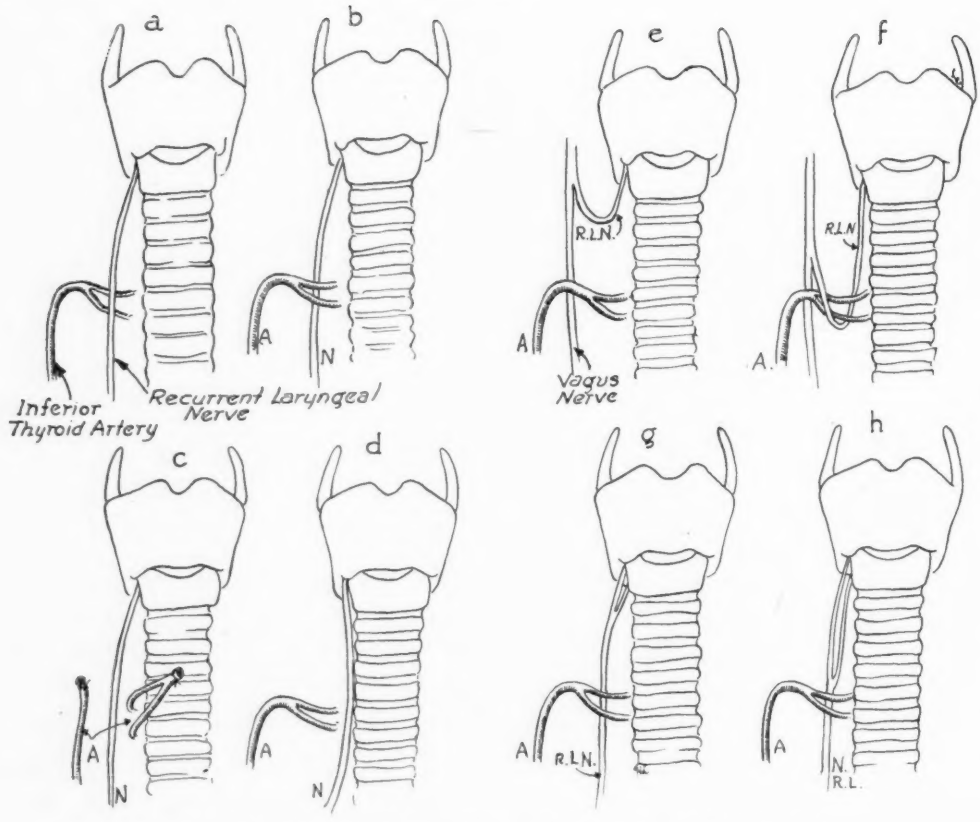

Fig. 7.—The locations and abnormalities of the recurrent laryngeal nerve.

a, The recurrent laryngeal nerve passes over the inferior thyroid artery. A nerve in this location is demonstrated and also injured more easily than the one which passes under the inferior thyroid artery. When the thyroid gland is lifted out of its bed, the nerve also is lifted up as the artery is pulled upward in the mid-portion of the gland.

b, The most common position of the recurrent laryngeal nerve. The inferior thyroid artery must be found first, and then the nerve is demonstrated as it passes under or over it.

c, The inferior thyroid artery is severed and ligated at both ends. In a difficult procedure this facilitates demonstration of the recurrent laryngeal nerve from its point of emergence in the mediastinum to its point of entrance into the larynx.

d, The position of the recurrent laryngeal nerve in intrathoracic goiter. As the thyroid adenoma descends into the mediastinum, it tends to push the recurrent laryngeal nerve against the trachea until it is sometimes so adherent that demonstration is difficult unless this occasional anomalous position is recognized.

e, The recurrent laryngeal nerve does not descend into the mediastinum, but comes straight across from the vagus to enter the larynx beneath the inferior constrictor muscle.

f, The recurrent laryngeal nerve descends as far as the inferior thyroid artery and ascends behind it to its point of entrance into the larynx.

g, Extralaryngeal division of the recurrent laryngeal nerve.

h, Extralaryngeal division extending as low as the inferior thyroid artery.

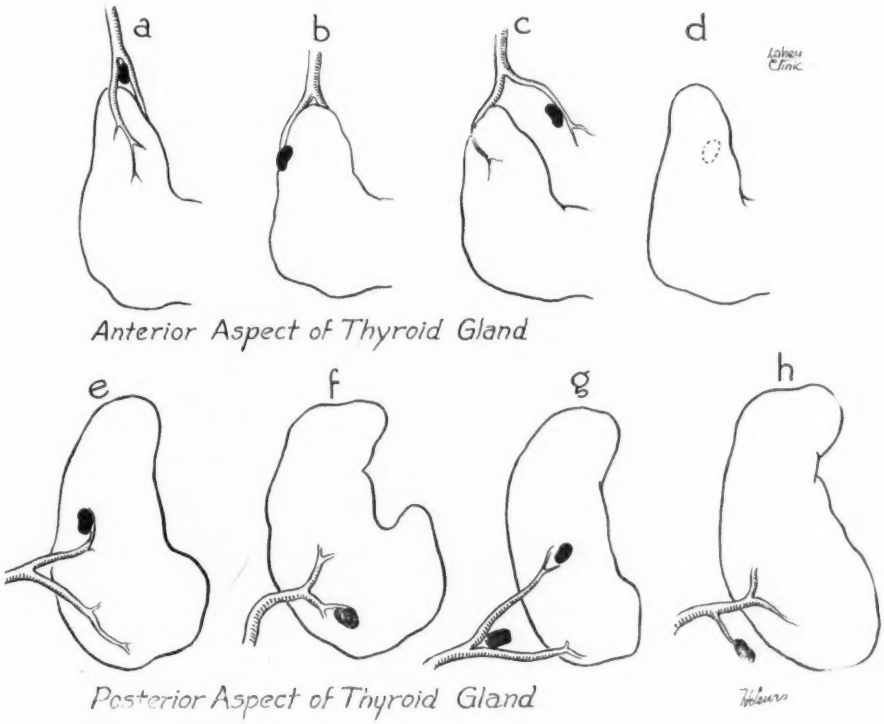

Fig. 8.—The anterior and posterior aspects of the thyroid gland showing the various positions in which a parathyroid gland has been demonstrated. *d*, The dotted line shows the parathyroid gland against the larynx. This type can easily be removed unless it is carefully visualized as the upper pole is pulled away from the larynx. *h*, The type of parathyroid gland with a separate terminal branch of the inferior thyroid artery. If an adenoma of the parathyroid gland cannot be found, the entire course of the inferior thyroid artery should be carefully demonstrated, preserving all its branches. If a branch comes off the main trunk downward, it should be followed, since it will often lead to a parathyroid adenoma in the mediastinum.

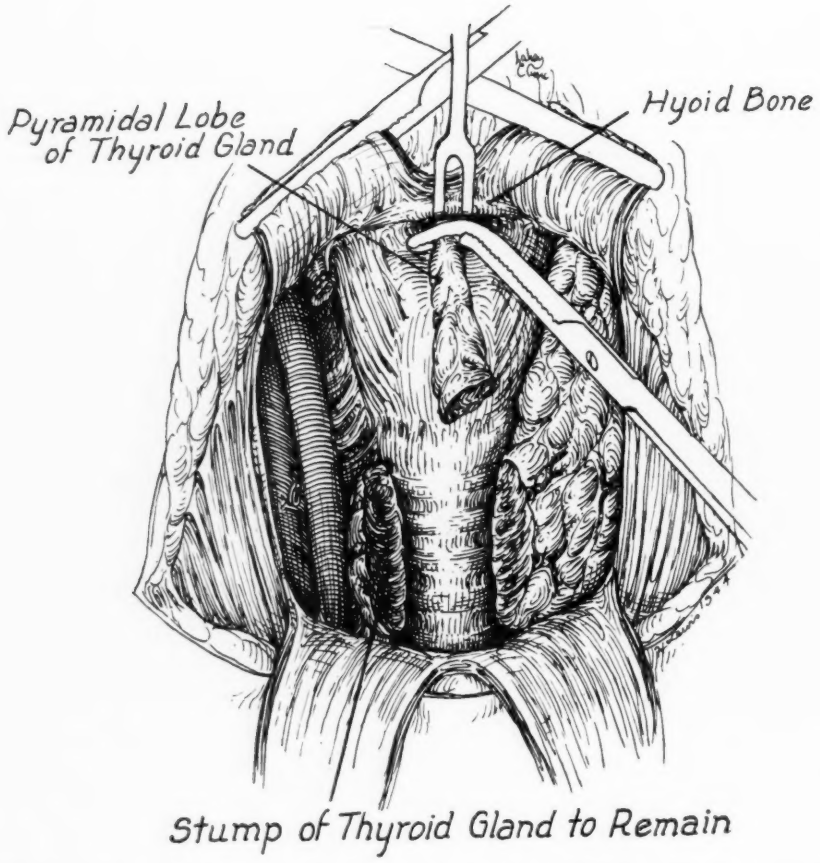

Fig. 9.—The removal of the pyramidal lobe, which is present in a large number of cases. If the pyramidal lobe is not removed in a patient with an exophthalmic goiter, it may enlarge sufficiently to cause persisting hyperthyroidism and an unsightly tongue of hyperplastic tissue in the central portion of the neck. Therefore, in subtotal thyroidectomy a careful search should be made for the pyramidal lobe, following it well up above the notch of the thyroid gland to the point where it disappears or ceases at the hyoid bone. In our experience in the removal of the pyramidal lobe, section of the hyoid bone has been unnecessary.

On the right side the superior thyroid artery and vein have been ligated. The tie here is often so close to where the vessel is cut that with coughing it can blow off. When the operation is completed, therefore, this ligated stump of the superior thyroid artery and vein should be regrasped and ligated a second time above the first ligature. When the superior thyroid artery is thus twice ligated and the inferior thyroid artery is ligated as a trunk (Fig. 5), serious secondary arterial hemorrhage is unlikely.

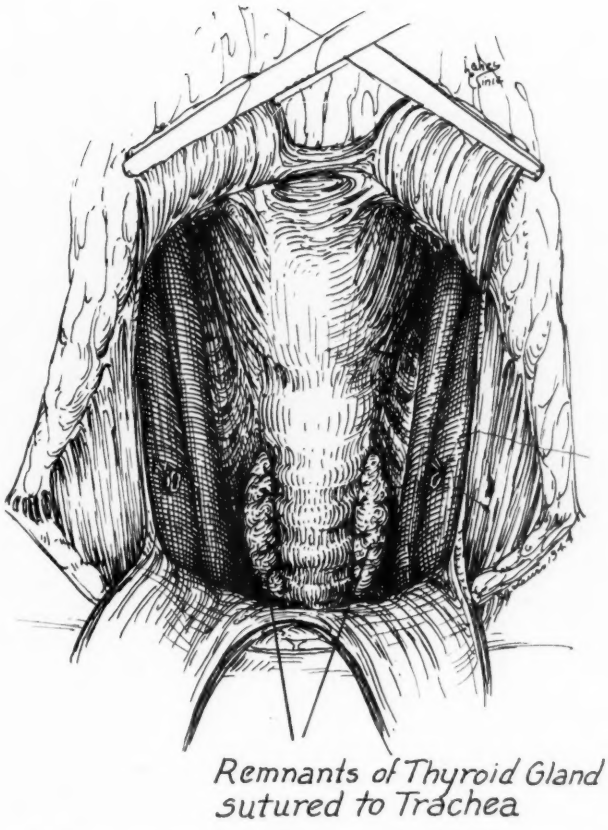

Fig. 10.—Completed reconstruction of the thyroid gland. The small stumps of thyroid tissue shown behind the dotted line in Fig. 5 are so sutured against the trachea with fine 00 catgut that the oozing surface is buttressed against the trachea. All bleeding of an oozing character is controlled, and drainage is unnecessary. Again, note the height to which the skin and muscle flaps are elevated in order to obtain high exposure.

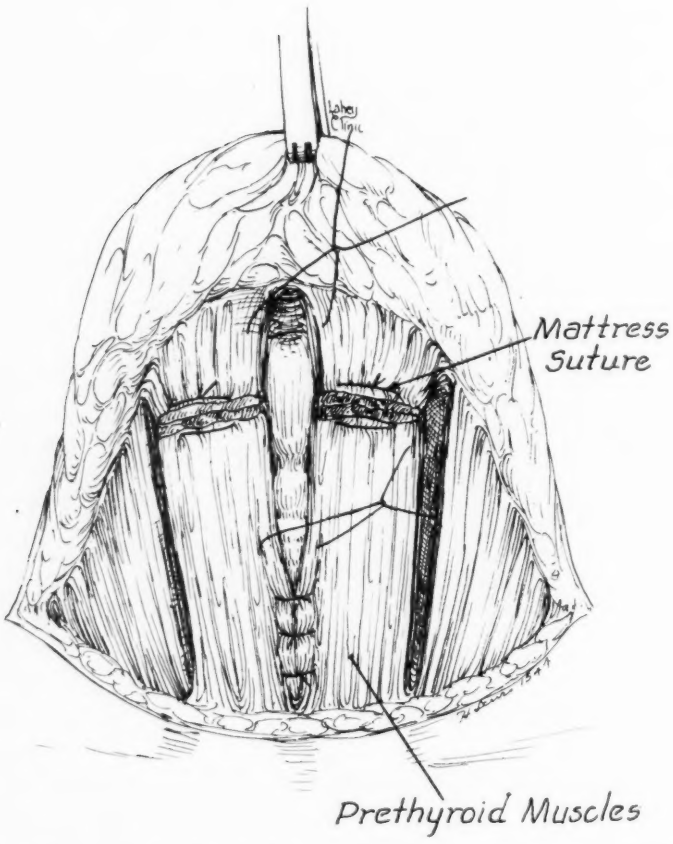

Fig. 11.—The method of suturing muscles with mattress sutures, the height to which they are sutured, and the accurate closure of the muscles in the midline are shown. Unless the muscles are accurately closed in the midline, the skin flap will become adherent to the trachea, will ascend and descend with swallowing, and will thus result in an ugly disfigurement. The sutures are well above the point of innervation and do not involve the same level as the skin suture.

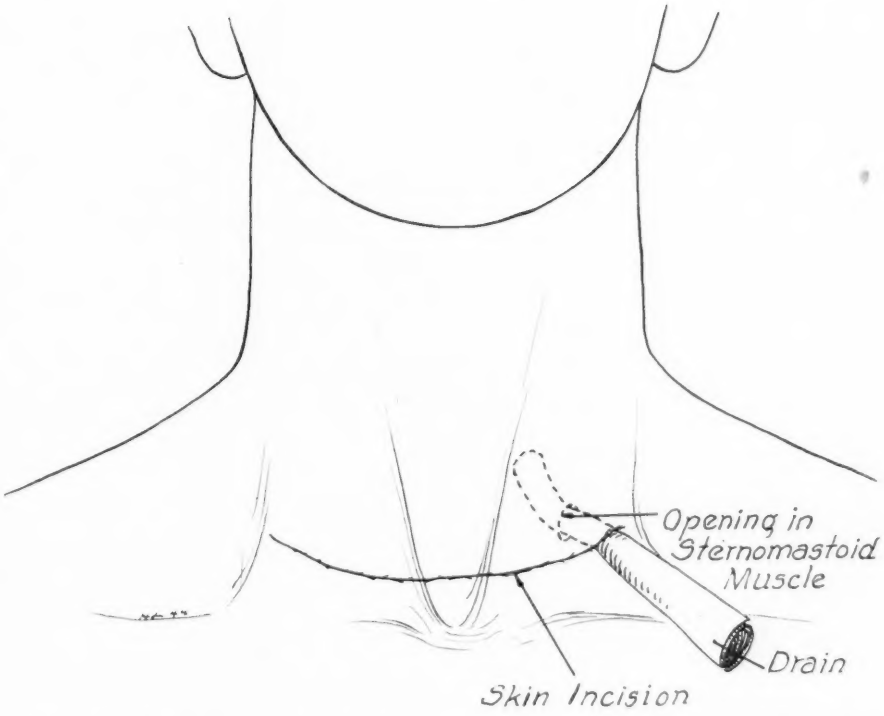

Fig. 12.—Drainage occasionally is necessary in recurrent hyperthyroidism after second stage hemithyroidectomy. The drain is not inserted in the midline in a counterincision, as has often been proposed, because this produces disfigurement and the scar cannot be covered with a necklace. It is placed at the end of the skin incision, which will close when the drain is withdrawn, and pierces the sternomastoid muscle. Since it is at the outermost portion of the wound, adhesions will not occur between the trachea and the skin. When the drain is withdrawn from its opening in the sternomastoid muscle, the muscle will then be interposed in the scar in the bed of the thyroid gland to prevent fixation of the scar of the skin to the thyroid bed scar.

Fig. 13.—The method of freeing an intrathoracic goiter from the mediastinal tissue. Note that the index finger is inserted into the mediastinum outside the capsule of the adenoma and is swept around until the adenoma is freed from the pleura and cellular tissue in the mediastinum. This is the first step in removing an intrathoracic goiter which is often of such diameter that it cannot be made to pass through the aperture of the superior thoracic strait.

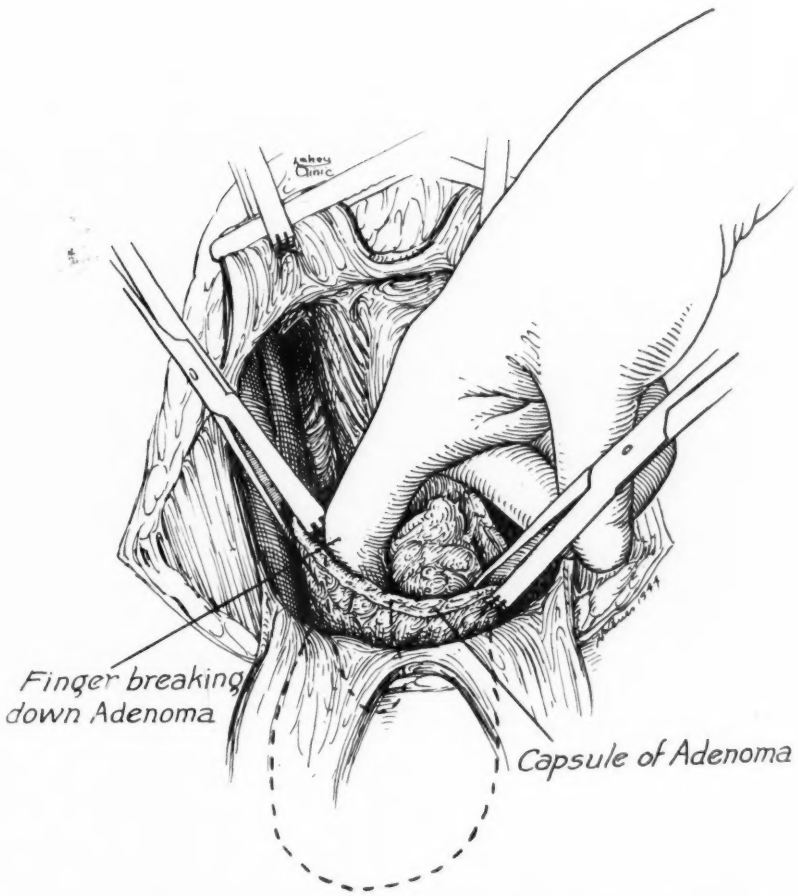

Fig. 14.—After the upper third or half of the adenoma has been freed from the surrounding cellular tissue and pleura in the mediastinum (Fig. 13), it is lifted with double hooks just above the clavicle and its top is incised. This leaves the soft contents exposed. Unless the tumor is carcinomatous and so of solid consistency, the index finger can be inserted into the center. Its contents, which are usually seminecrotic or semicystic, can be broken down and scooped out, and its fluid sucked out, thus decreasing its diameter. With gradual traction upward on the double hooks, which are inserted in the capsule, the adenoma is lifted and further separated with the index finger outside of the capsule (Fig. 13), freeing it from the pleura, thus further breaking down its center, with additional delivery. In this manner, enormous intrathoracic goiters can be delivered from the mediastinum without removing the manubrium or the clavicle.

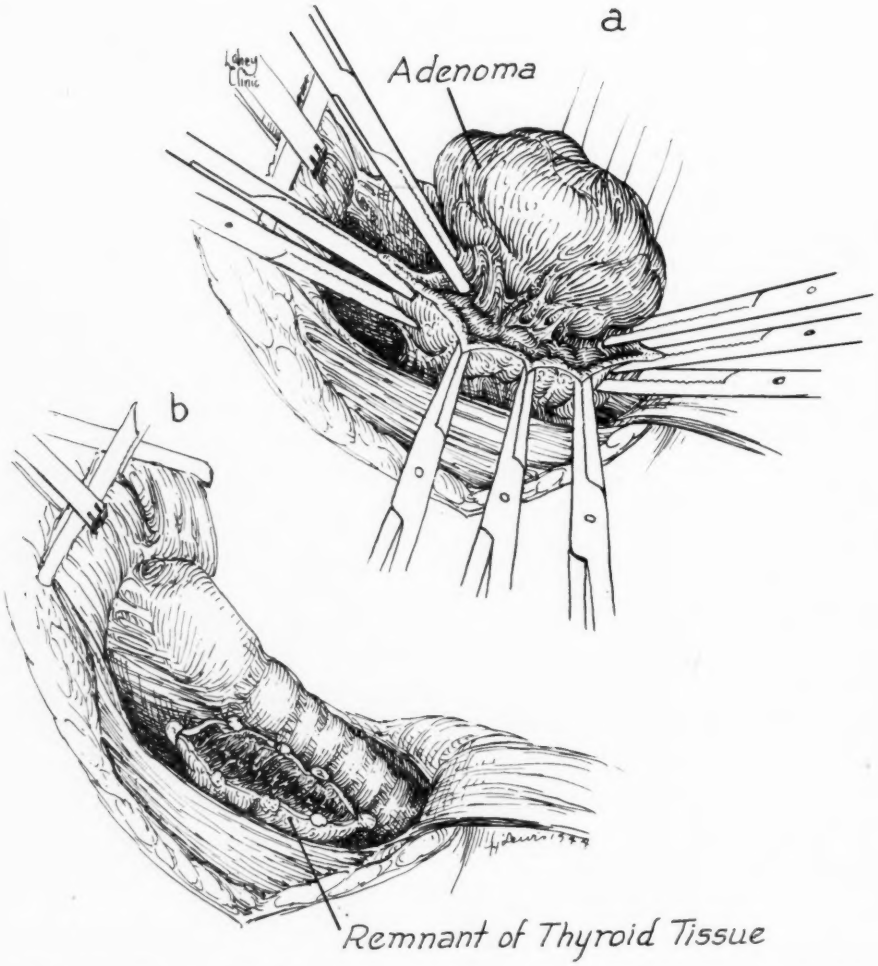

Fig. 15.—The method of removing a discrete adenoma of the thyroid gland is different from a subtotal thyroidectomy for exophthalmic goiter.

a, An Ochsner clamp with another small clamp over it is placed on the upper portion of the nonadenomatous part of the gland and in the same manner on the lower portion. Next clamps are placed along the outer side of the adenoma, where normal thyroid tissue covers it, and this layer is cut, so that the adenoma literally can be shelled out of the body of the thyroid tissue. As the adenoma is shelled out toward the midline, a small envelope of thyroid tissue of varying thickness is retained along the trachea until all the adenoma is excised.

b, The edges of the thyroid gland can be brought together to reconstruct a good lobe of thyroid tissue.

The recurrent laryngeal nerve is not shown, but in this operation, as in subtotal thyroidectomy for exophthalmic goiter, the inferior thyroid artery is ligated to protect against later secondary hemorrhage, and the recurrent laryngeal nerve is demonstrated. The wisdom of dissecting the recurrent laryngeal nerve in the removal of a discrete adenoma often has been questioned, but in this operation it is even more important than in the removal of an exophthalmic goiter. A discrete adenoma often so completely occupies the substance of the thyroid gland that but a thin shell of normal thyroid tissue remains between the back wall of the discrete adenoma and the nerve. Thus, the recurrent laryngeal nerve is in close contact with this thin shell of tissue and with the capsule of the adenoma. Because of this, it is easy to penetrate the thin shell of thyroid tissue behind the adenoma and thus unknowingly pinch the recurrent laryngeal nerve.

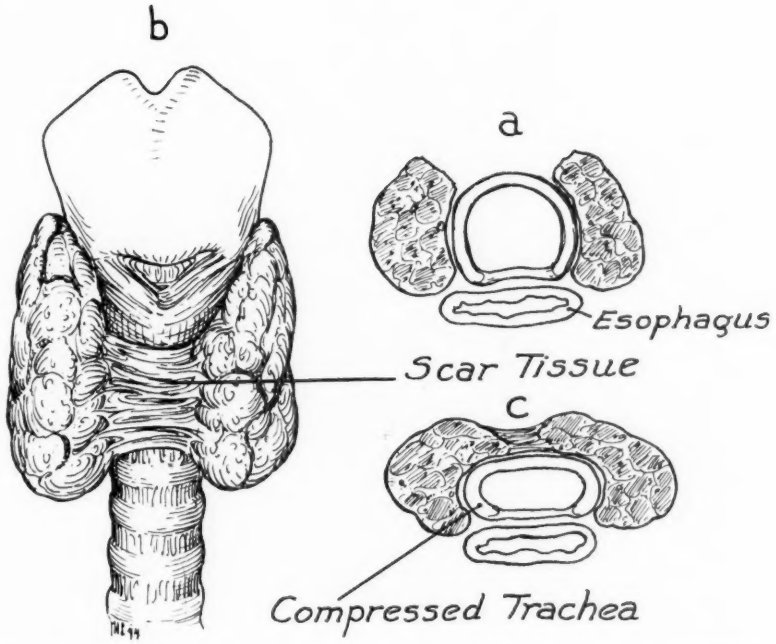

Fig. 16.—The incorrect method of removing the isthmus in patients with thyroiditis who complain of constriction of the trachea due to organization of round-cell infiltration. No attempt has been made to prevent scar tissue formation between the two cut ends of the remaining lobes; thus contraction causes further constriction.

a, The isthmus has been removed.

b, The development of scar tissue between the two remaining lobes over the trachea.

c, Compression of the trachea results from contraction of scar tissue replacing removed isthmus and joining the two lateral lobes. When this occurs the trachea sometimes is decreased sufficiently in size to interfere seriously with the intake of an adequate amount of oxygen.

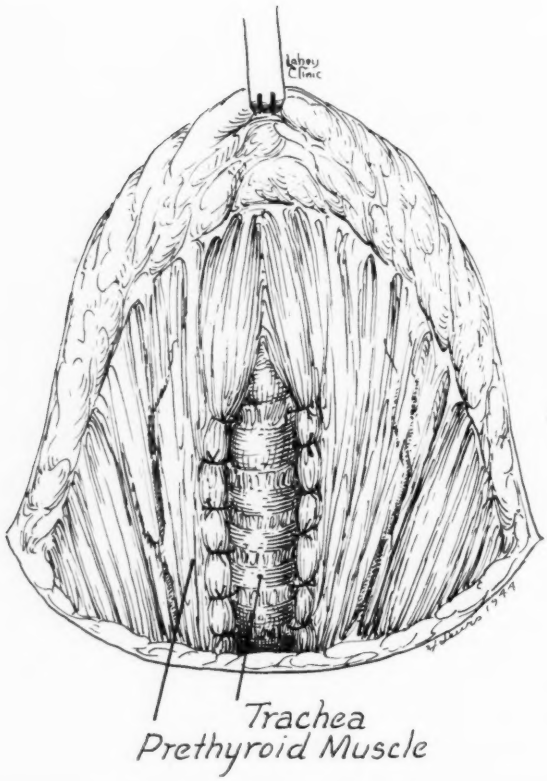

Fig. 17.—The correct method of removing the isthmus for constricting thyroiditis. The suture of the prethyroid muscles is shown over the stump of thyroid tissue on each side where the isthmus has been removed. The prethyroid muscles are attached to the trachea, thus completely segregating the two segments of thyroid gland beside the trachea and preventing the formation of scar tissue between them.

Surgery is rarely necessary in thyroiditis. Occasionally, however, as the result of the entire trachea being grasped by an enlarged thyroid involved in thyroiditis, a considerable sense of constriction results. This can be relieved by removal of the isthmus. Further constriction can be avoided by suturing the prethyroid muscle to the trachea over the sutured ends of the remaining thyroid tissue in each lobe, thus preventing the formation of any scar tissue between the two separated lobes.

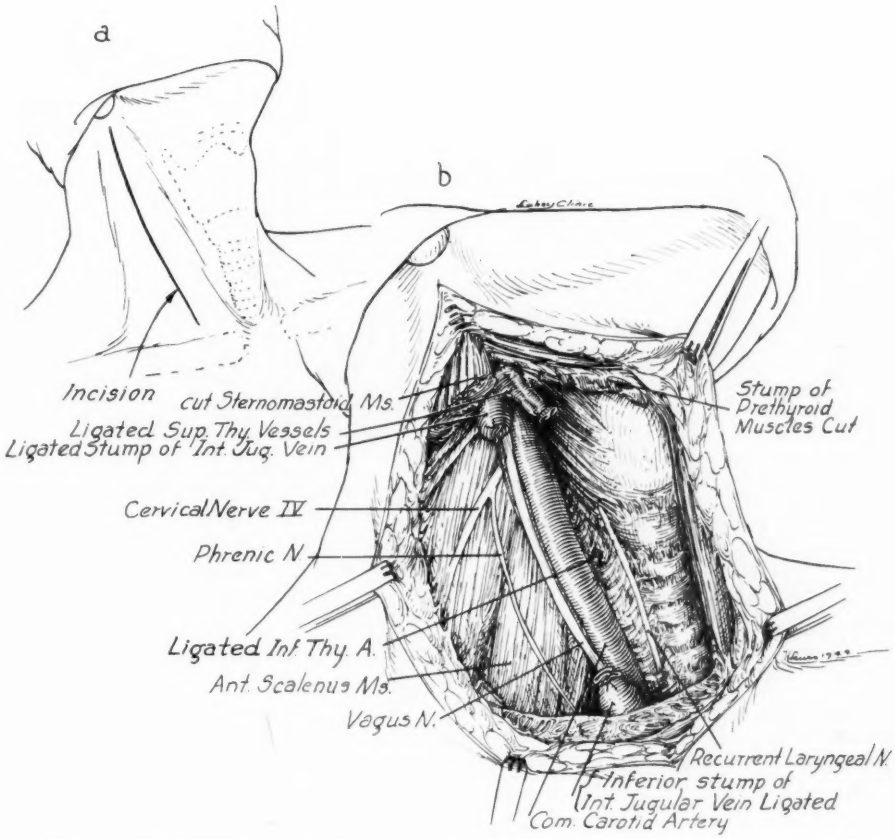

Fig. 18.—Radical removal of one lobe of the thyroid gland for cancer, together with removal of the sternomastoid muscle, the internal jugular vein, the thyroid veins, and any lymphatics.

a, The incision and *b*, the anatomic relationships following radical removal of one lobe and the isthmus of the thyroid gland for an adenoma. Malignancy had penetrated the capsule of the adenoma and had involved the parenchyma of the thyroid gland. The incision can be longitudinal or can be carried across the neck as a fish-hook type.

Since malignancy of the thyroid gland has a definite tendency to invade veins, it has always been our practice, when carcinoma has penetrated the capsule of an adenoma and involved the parenchyma of the gland on one side, to do a radical dissection, ligating the internal jugular vein high and low and severing the sternomastoid muscles high and low. The entire sternomastoid muscle, tributary veins, regional lymph nodes, and the entire right lobe and isthmus of the thyroid gland containing the malignant degenerated adenoma are then removed in one block. Included with the block of removed tissue are the prethyroid muscles.

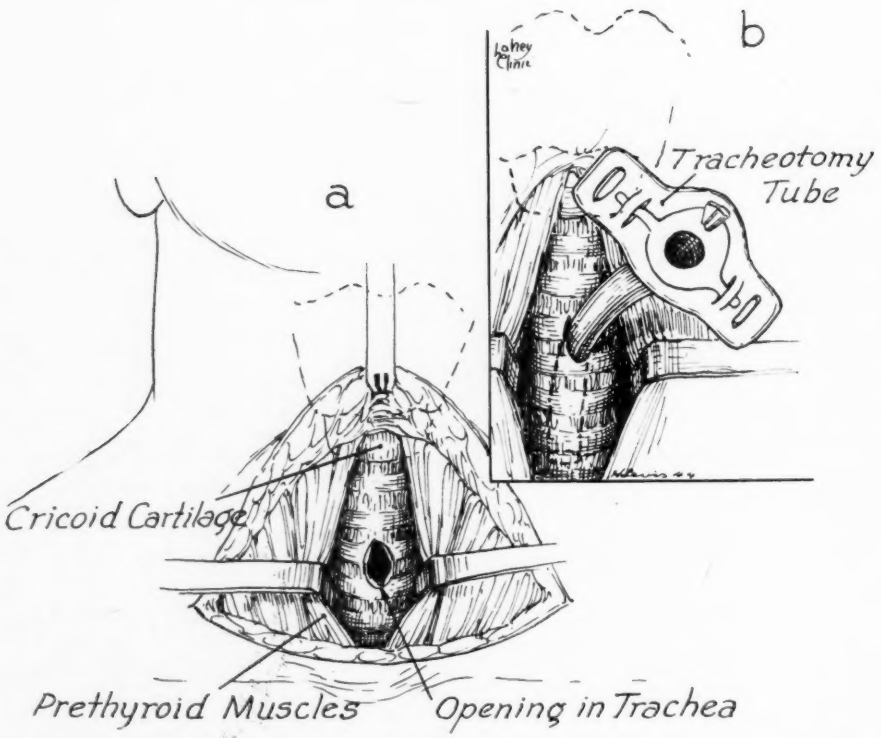

Fig. 19.—A tracheotomy is occasionally necessary to save the thyroidectomized patient's life. Edema or pressure upon the trachea may be so severe that the patient is unable to maintain an intake of oxygen sufficient to avoid a dangerous state of anoxemia. When the surgeon begins to think of the possibility of a tracheotomy, that is the time seriously to consider performing one.

Contrary to expectations, we have never seen any serious degree of infection occur in the cellular tissue of the neck or even in the mediastinum following tracheotomy after removal of an intrathoracic goiter.

A tracheotomy should not be performed at the easiest point, that is, near the level of the cricoid cartilage, which is shown in *a*. The trachea is narrowest here, and scarring and stricture are apt to occur. A tracheotomy should be low, between the third and fourth rings. A small amount of cartilage should be removed, so that an adequate opening to admit the tube is obtained.

In subtotal thyroidectomy for hyperthyroidism or for toxic adenoma, the isthmus is removed. This adds to the amount of thyroid tissue which is removed and also leaves the trachea so bared that a postoperative tracheotomy, if necessary, can be performed quickly and easily.

We have no hesitancy in doing a tracheotomy if there is any question of the patient's obtaining an adequate amount of oxygen. The tube can be removed on the fourth or fifth day, and the trachea closes quickly without incident. There usually is little interference with the scar, and even if there is, it is infinitely better to have to revise the scar than to endanger the patient's life for lack of oxygen, particularly in the postoperative stages of thyroidectomy for severe hyperthyroidism.

DRAINAGE IN THYROIDECTOMY

DONALD GUTHRIE, M.D., F.A.C.S., AND
IRWIN SCHIMMEL, M.D., SAYRE, PA.

THE problem of drainage versus nondrainage in thyroidectomy is one which always arouses debate among surgeons. Ever since the days of Kocher, the father of modern thyroid surgery, drainage was practiced by practically all of the early American surgeons with the exception of Halsted, who advocated the use of silk and who believed that drainage of the wound was unnecessary. Drainage was necessary because heavy catgut was employed to secure hemostasis. As a result of the exudative response of the tissues to catgut, these wounds all drained freely for a considerable length of time.

When catgut was used routinely at the Guthrie Clinic, all of the wounds were drained with one or more rubber tubes which were placed in the goiter bed and were allowed to remain about forty-eight hours. Large substernal and intrathoracic cavities were drained with three or four tubes which remained in place for four or five days. All of the wounds continued to drain approximately fifteen days, necessitating a hospital stay for the patient of at least sixteen days after the operation.

Before discontinuing the catgut technique, an attempt was made to use finer catgut in order to eliminate drainage. However, this was unsuccessful because of the tissue response to the absorbable suture material. A compromise technique using fine catgut to suture the remnant and silk for all ligatures was tried; with this method we were able to close 62 per cent of the wounds without drainage. However, this technique was soon supplanted by an all-silk thyroidectomy. With the advent of the nonabsorbable suture technique, wound drainage became unnecessary and, we believe, fraught with risk because of the danger of secondary infection through the open portion of the wound.

Following the report of Meade and Oschsner, in 1940, in which cotton as a suture material was proved to cause less tissue reaction and earlier healing than silk, cotton replaced silk as the nonabsorbable suture material for all thyroidectomy wounds. With this technique, the patient's temperature in the average case is usually normal within forty-eight hours. One-half of the clips are removed within twenty-four hours and the remainder at the end of forty-eight hours. The wound dressing may be discarded with safety at the end of ninety-six hours and the average postoperative stay in the hospital is reduced to

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nine days. No further dressings are necessary and six days are removed from the post-thyroidectomy hospitalization.

In reviewing our results since the adoption of the nondrainage technique, we have found that in a series of 580 cases, it was necessary to use a drain in only 8. Furthermore, none of these drains was placed in the goiter bed, all being inserted under the skin flap as advocated by Coller. In this series there were three wound infections, two being of a minor nature. In one case the skin edges opened completely and a secondary closure was necessary. An occasional patient will require the removal of a sterile cotton knot. However, since we have used the very fine No. 80 cotton in the skin flap, this procedure has been necessary in but two or three patients.

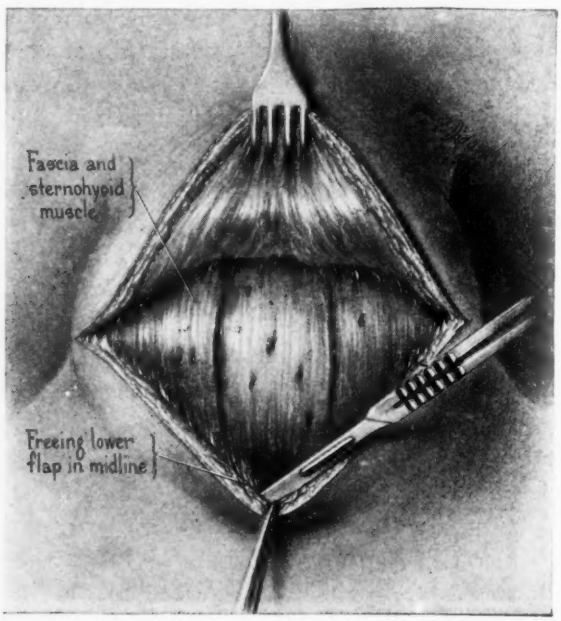

Fig. 1.—Freeing the lower flap in the midline only over the suprasternal notch. (Illustrations by permission of Surg., Gynec. & Obst., from "A Technique of Thyroidectomy Permitting the Use of Silk" by Donald Guthrie and Merle J. Brown 68: 801-809, 1939.)

Mediastinitis is feared by many surgeons following the removal of substernal or intrathoracic goiters if drainage is not employed. A few of them pack these cavities with gauze. Such a procedure would seem to insure secondary infection rather than to prevent it. We have not used drainage in any of these cases and have seen no untoward effects as a result. Two of our patients, in whom drainage was done when catgut was used, developed mediastinitis due to secondary infection and died as a result.

There are a few technical points which must be employed if the surgeon is to use the nondrainage method successfully. In the first place all dissection must be sharp with a constant regard for tissue

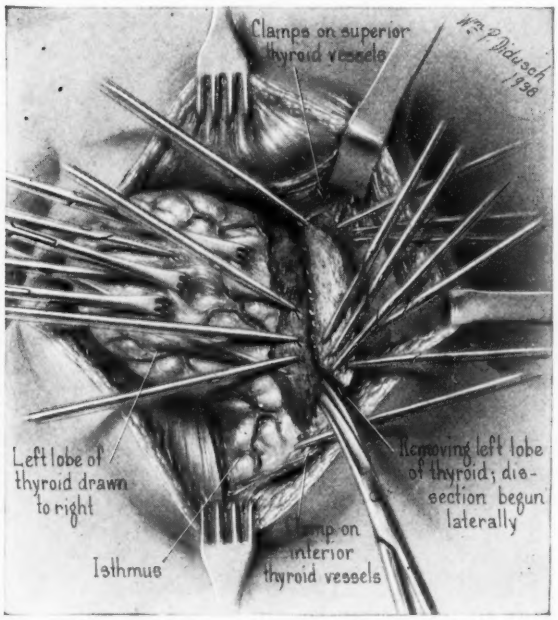
Clamps on superior thyroid vessels
Left lobe of thyroid drawn to right
Removing left lobe of thyroid; dissection begun laterally
Isthmus
Clamp on inferior thyroid vessels

Fig. 2.—Dissection of the lobe continued to show what should be the size of the thyroid remnant that is to be left in situ.

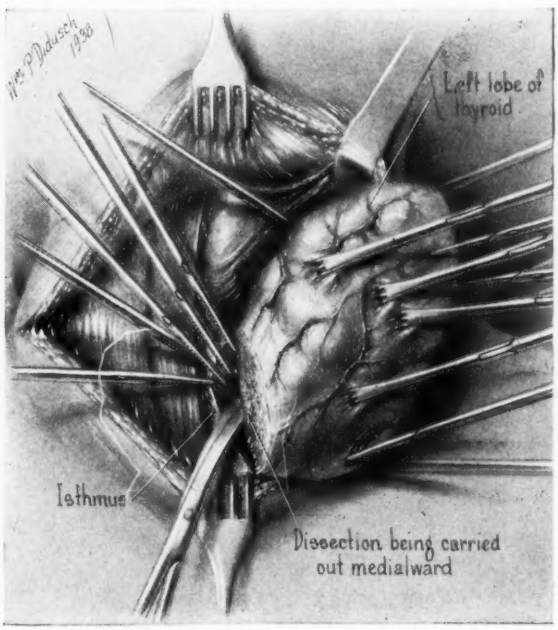

Fig. 3.—Dissection of the lobe from the trachea showing remnant of the gland left along the trachea.

because blunt dissection encourages edema and wound exudation. Mass ligatures must not be employed and hemostasis must be absolute. It is obvious that wide dissection of the lower skin flap is unnecessary for exposure and merely provides additional dead space where serum may collect (Fig. 1). In accordance with the principles outlined by Lahey, after all the vessels have been ligated, the remnant which has

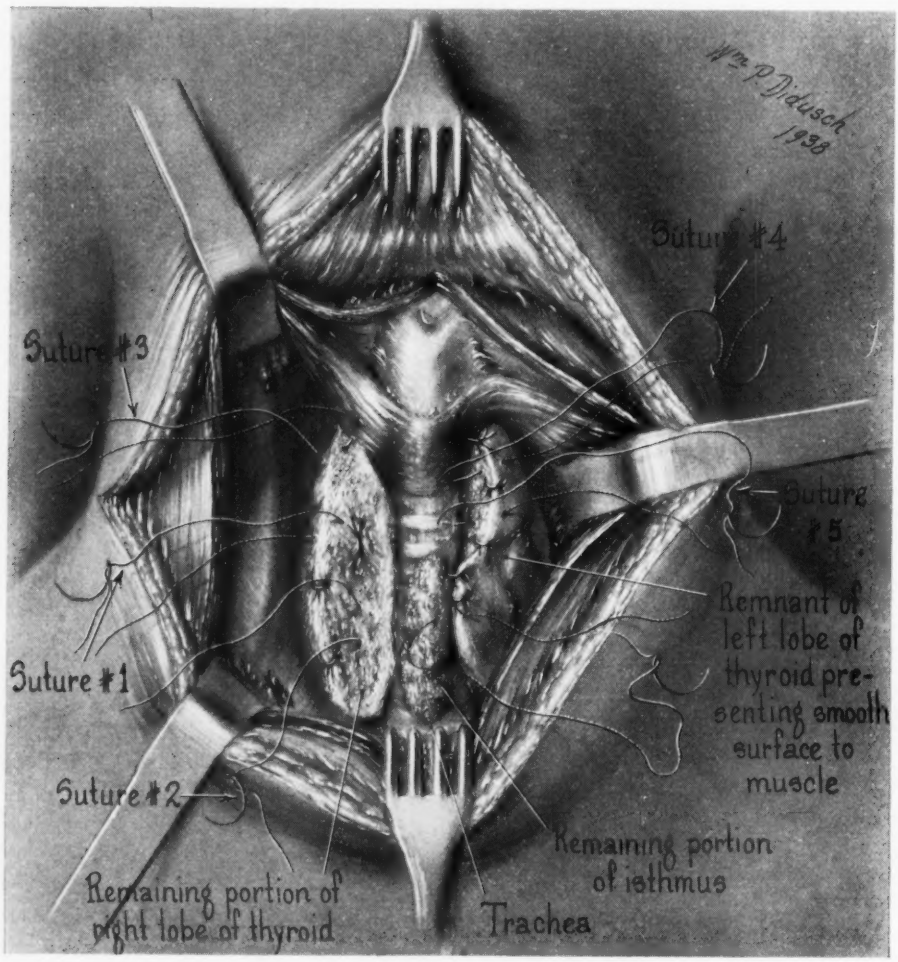

Fig. 4.—Method of controlling hemorrhage from the remnant by two rows of the interrupted fine silk sutures placed at different levels in the long axis of the neck. Interrupted sutures are placed through the edges of the remnant and the fascia and the thyroid tissue of the trachea inverting the outer surface of the remnant to conceal its incised surface.

been carefully plotted is rotated medially toward the trachea. Its lateral portion is then sutured to the small bit of thyroid gland which has been intentionally left attached to the trachea (Figs. 2 and 3). This brings the cut and oozing surface of the gland against the trachea, providing a valuable adjunct in hemostasis (Fig. 4). A dry wound is the sine qua non of the nondrainage method of thyroidectomy. In ad-

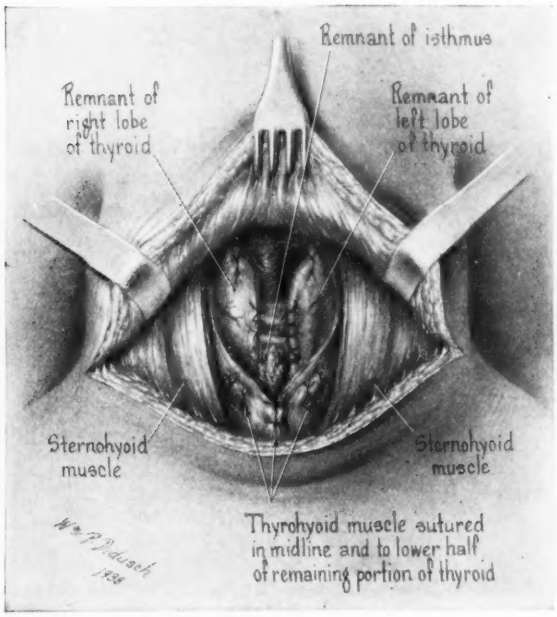
Remnant of isthmus
Remnant of right lobe of thyroid
Remnant of left lobe of thyroid
Sternohyoid muscle
Sternohyoid muscle
Thyrohyoid muscle sutured in midline and to lower half of remaining portion of thyroid

Fig. 5.—Sternothyroid muscles are sutured at the midline and to the lower portion of the remnant.

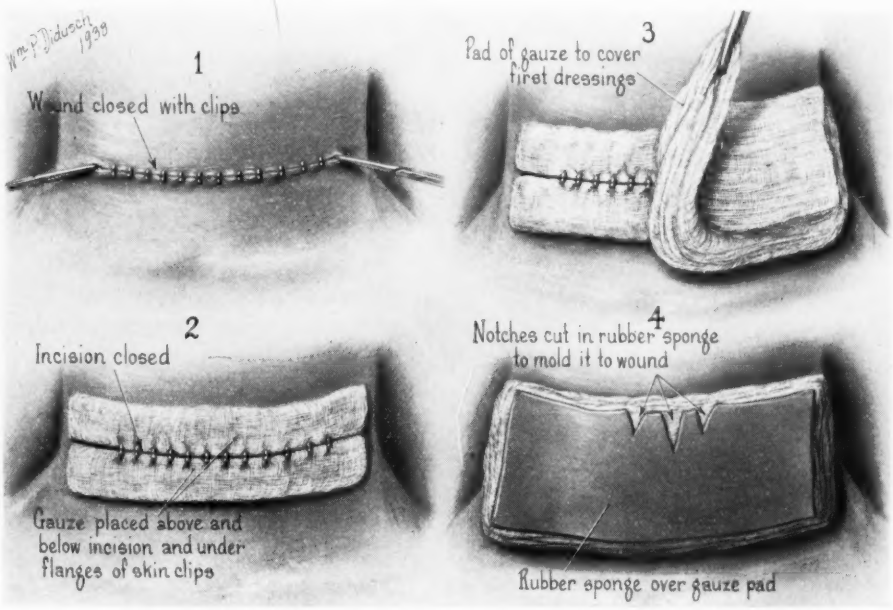
1
Wound closed with clips
2
Incision closed
Gauze placed above and below incision and under flanges of skin clips
3
Pad of gauze to cover first dressings
4
Notches cut in rubber sponge to mold it to wound
Rubber sponge over gauze pad

Fig. 6.—Illustrating the method of dressing the wound.

dition, we believe that suturing the right and left sternothyroid muscles together in the midline and, if necessary, to the base of the remnant, is valuable in further insuring against oozing and bleeding (Fig. 5). The sternohyoid muscles are sutured in the midline and then the flap is carefully inspected to be certain that there is absolute hemostasis.

As an added precaution to prevent flap oozing and to aid in obliterating dead spaces, we employ a notched rubber sponge over the wound. This is held in place by two one-inch adhesive strips and the entire neck is wrapped with wide gauze bandage. We employ this technique in all cases. (See Fig. 6.)

SUMMARY

Drainage in thyroidectomy is unnecessary if a nonabsorbable technique is employed.

Careful hemostasis and special care for the remnant are responsible for the success of this method.

In our experience, cotton is highly satisfactory and makes undrained thyroid wounds possible.

By avoiding drainage, we have been able to reduce the average post-thyroidectomy hospital stay from sixteen to nine days, an economy for both hospital and patient.

A NEW PLAN IN THE OPERATIVE TREATMENT OF PATIENTS WITH SEVERE HYPERTHYROIDISM

The Use of Spinal Anesthesia as an Adjunct to Their Preoperative Care

Major Charles E. Rea,* Medical Corps, A.U.S.

IT IS the purpose of this communication to report briefly the employment of spinal anesthesia as an adjunct to the operative management of severe hyperthyroidism. This plan has been employed in twenty cases with real satisfaction. Whereas, the use of spinal anesthesia in the management of postoperative thyroid storm has been described previously from this clinic, and whereas Crile and Bartels, Stuart, and Johnson have employed spinal anesthesia for a similar purpose, the basis of the proposal described herein is predicated on the thesis that an effective spinal anesthesia, which would inhibit medullary adrenal releases during the operation, would help to forestall the occurrence of immediate severe postoperative reactions. It is not the intent to secure anesthesia to a level (second to fourth cervical segment) which would permit the operation being done under this agency alone. On the contrary, a somatic analgesia to about the fourth dorsal segment is derived with the use of spinal anesthesia, the analgesic for the performance of the operation upon the neck being obtained with the use of other agents—usually a combination of pentothal and cyclopropane.

MODE OF MANAGEMENT

The usual considerations which have guided surgeons in the management of patients with severe hyperthyroidism constitute an integral part of the therapeutic program. Briefly the following are given careful notice:

1. *The Use of Lugol's Solution.*—Of all the components of preoperative treatment of patients with severe hyperthyroidism, there is none so abused as the use of Lugol solution. When iodine first came into general use in the early 1920's, the answer to the goiter problem was thought to be found. However, this has proved not to be the case in the ensuing years. Empirically, one gives five to ten drops of Lugol's solution three times daily to patients with hyperthyroidism. One should never give Lugol's solution for more than two-week periods without evaluating the clinical status of the patient. The practice of giving Lugol's solution for months to goiter patients is to be condemned, as it is not only unnecessary but also may confuse the clinical picture.

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The practice of treating children or adults with mild hyperthyroidism with small doses of iodine over a long period of time has been advocated by some clinicians. In our opinion this is a dangerous form of therapy for the reasons just mentioned, and it puts a big responsibility on the physician prescribing the treatment. Thyroidectomy is a safer and surer method of treatment. It is our policy to be more conservative with children developing mild degrees of hyperthyroidism about the time of puberty. Two instances of mild exophthalmic goiter in children have come to our attention, in which spontaneous remission of symptoms after puberty occurred. Older children with hyperthyroidism have been subjected to thyroidectomy similar to that in adults.

At this clinic Lugol's solution is given to patients with hyperplastic goiters and also to those with nodular goiters with hyperthyroidism, both pre- and postoperatively. In our experience it is not necessary to give iodine medication to patients with nodular goiter without hyperthyroidism, either before or after operation. Rather disturbing, however, is the fact that of 155 patients with "nontoxic adenoma of the thyroid" operated upon at the University of Minnesota Hospitals between 1933 and 1940, who had not received Lugol's solution preoperatively, three showed degrees of thyroid storm postoperatively. These were probably cases of latent hyperthyroidism, not diagnosed clinically. For this reason, it is my personal opinion that it does no harm to give the majority of patients with nontoxic adenomas of the thyroid Lugol's solution before operation. The question of what percentage of nodular goiters without hyperthyroidism will be made toxic by the use of iodine is important (so-called Jodbasedow). It is said that in Kocher's clinic the use of iodine for sterilizing the skin in goiter operations was forbidden. Kocher's successor, de Quervain, listed thirty-three cases of Jodbasedow in nine years. However, Dr. Carl Rice, at the goiter clinic at the University of Minnesota Hospitals, has purposely treated patients with nodular goiter without hyperthyroidism with low doses of Lugol's solution (one to two drops a day) up to a period of two years, and has not seen one who was made toxic by the iodine medication. Further, there are no statistical studies to show that there are more cases of toxic goiter developing among persons who took iodine for nodular goiter than among goitrous persons who did not take iodine (McClendon). It is my opinion that some instances of Jodbasedow are really cases of latent hyperthyroidism, flared up by stimuli other than the iodine. The whole question of Jodbasedow merits a complete and critical reinvestigation before definite conclusions are warranted, however.

2. *Mental and Physical Rest.*—By means of controlled environment and sedation, a state of mental and physical rest can be obtained in patients with hyperthyroidism. For sedation, phenobarbital, from ½ to 1 gr. three times a day, are used with seconal, from 1½ to 3 gr., at night. At this clinic the patients are allowed bathroom privileges.

The mental attitude of the patient toward his condition and the operation are very important because regardless of what the laboratory tests may show and how satisfactory his physical condition may seem, if the patient is nervous and apprehensive he is not a good candidate for operation.

3. *Diet.*—Patients with hyperthyroidism should be given a high caloric diet. A high protein and a high carbohydrate component should be stressed. The patient's weight is one of the best checks on how he is progressing. A patient with hyperthyroidism who is gaining weight, regardless of what the basal metabolic rate may be, shows that he is improving under therapy. We have checked plasma proteins of four patients with severe hyperthyroidism and have found them to be within normal ranges.

4. *The Use of Other Drugs.*—The reports to date concerning the use of thiouracil seem to indicate that that drug is of value in the preoperative management of certain patients with hyperthyroidism. Thiamine chloride is given routinely to patients with hyperthyroidism at this clinic. Those whose clinical condition does not improve in spite of Lugol's solution (iodine-fast) are often improved by attention to rest, diet, sedation, or thiamine chloride. In six iodine-fast patients with goiter, the use of diiodotyrosine gave no more benefit than that obtained with Lugol's solution.

5. *Operation on Thyroid Gland.*—The following factors should be taken into consideration before operating on the thyroid gland: the patient's age, the size of the gland, the response to Lugol's solution, the duration of the hyperthyroidism, the basal metabolism rate, the pulse, the gain in weight, and the patient's general physical and mental condition. The procedure to be used should be decided in the surgeon's mind in the patient's room *before* operation and not at the operating table. If, from an evaluation of the patient's condition, just a ligation of the superior poles of the thyroid gland or a lobectomy is agreed upon, it is inviting disaster to proceed further just because the patient stood the stage procedure well. Moreover, if the patient begins to react badly while the surgeon is doing the procedure contemplated before operation, it is best to do the minimum and, if the operation has not gone too far, to close the wound as quickly as possible. The three fatalities that have occurred in this clinic during the past three years in thyroid patients (out of a total of 308 operations) have been due to failure to observe one or both of these two rules.

Since the whole rationale of thyroidectomy in hyperthyroidism is to shift the patient from a state of hyperthyroidism to one of hypothyroidism, hoping to hit a happy medium, one can realize how much the experience of the surgeon counts in judging how much of a thyroid should be removed. In severe thyrotoxic patients one aims to do a bilateral subtotal thyroidectomy in one or more stages. It is interesting to note how the stage procedure has passed from one of necessity

to one of election. At this clinic, a unilateral lobectomy has been the stage procedure of choice in the severely thyrotoxic patient. A right subtotal lobectomy is usually performed first, with surgical removal of the left side being deferred until two to four weeks later. The use of local, general inhalation or intravenous anesthesia, or combinations of these, depends somewhat on the choice and temperament of the surgeon. Ether is a bad anesthetic for thyrotoxic patients, as it tends to produce pulmonary edema. Cyclopropane has been used as the chief inhalation anesthetic at this clinic, but is contraindicated if the patient has cardiac irregularity. Its chief value lies in the high oxygen content of the mixture.

At the University Hospitals the use of intravenous pentothal ("sneak thyroidectomy") has proved of value in patients with toxic goiter. The procedure is as follows: For two or three days before operation the patient is given 1,000 c.c. of 5 per cent glucose in saline solution intravenously. Since operations are performed in the afternoon at this hospital, the patient is given a liquid breakfast on the day of operation and intravenous glucose solution. No other preparation is made, so that the patient is unaware that he is to be operated upon that day. Just before operation, when the infusion has just about been completed, intravenous pentothal is given through the same infusion needle. The sleeping patient is taken to the operating room where the neck is prepared for operation and inhalation anesthesia is initiated.

THE USE OF SPINAL ANESTHESIA IN PATIENTS WITH SEVERE HYPERTHYROIDISM

In spite of careful preparation and preoperative care, some patients with severe hyperthyroidism have had degrees of thyroid storm postoperatively. To prevent such an occurrence, spinal anesthesia in the operative management of severe hyperthyroidism has been used. This idea was suggested from the good results following the use of spinal anesthetic in a case of thyroid crisis. This case has been reported in detail elsewhere. To date, spinal anesthesia has been used for three patients with thyroid crisis with good results at this clinic.

Because of the good results following the use of spinal anesthesia in cases of thyroid crisis, it was suggested that spinal anesthesia might be used as a preoperative measure in cases of severe hyperthyroidism. A report of the first patient so treated is given in detail because when operation was first attempted, without the spinal anesthesia (control), the patient had a severe reaction on the table.

CASE REPORT

C. G., aged 41 years, was admitted to the University of Minnesota Hospitals, Oct. 11, 1941. He gave a history of dyspnea, and fatigability since the winter of 1940 to 1941. Rather marked irritability had been noted by his wife about eight months previously. He noticed a mass in his neck and pounding of the heart

approximately three months prior to admission. In spite of an increased appetite, he had lost thirty-five pounds in the past year. He had noticed tremor of the hands for approximately two years.

On admission, the patient's temperature was 98.8° F., pulse, 100, respiration 20, blood pressure 138/60.

Physical examination revealed a well-nourished, well-developed white man who was rather hyperactive. There was a mild exophthalmos of both eyes and the thyroid gland was diffusely enlarged and firm. No bruit was heard. The heart was of normal size and the tone was forceful; no murmurs were heard. The lungs were clear to auscultation and percussion and there were no abdominal masses. A fine tremor of both hands was present. There was a staring expression of the eyes and definite lid lag.

The patient had received Lugol's solution, ten drops three times a day, since Sept. 28, 1941. He had also been given phenobarbital, 1½ gr. three times a day, and thiamine chloride, 1 mg. four times a day. Some difficulty was experienced in raising his caloric intake sufficiently, but with a 5,200 calorie, high carbohydrate, high protein diet, his hunger was relieved and he began to gain weight. Basal metabolic rate, Sept. 18, 1941, was plus 84 per cent; Oct. 2, 1941, plus 74 per cent; and Oct. 12, 1941, plus 51 per cent. The basal metabolic rate never went below this level at any subsequent test. His pulse rate was not excessive and consequently it was thought that lobectomy should be attempted.

Oct. 28, 1941, pentothal was given intravenously in his room and he was taken asleep to the operating room, where inhalation cyclopropane anesthesia was instituted. At the beginning of the operation the blood pressure was 140/80 and the pulse 120 per minute. After making the skin incision in the neck, his blood pressure was 180/90, but the pulse was still 120 per minute. On cutting through the platysma muscle and retracting the strap muscles of the neck, the blood pressure was found to be 220/100 and the pulse 160. Some of this untoward reaction was thought to be due to the cyclopropane, so this anesthetic was discontinued and only oxygen given. However, since the patient did not improve, the skin incision was closed and the patient transferred back to his room.

The patient had quite a stormy time for the first few postoperative days. Because of this reaction, it was decided to give him a course of deep x-ray therapy to the thyroid gland; he received 500 r/air to the anterior thyroid region and 250 r/air to the right and left lateral thyroid areas over a period of nine days from Nov. 5 to 14, 1941. His basal metabolic rate Nov. 7, 1941, was plus 53 per cent. The patient became somewhat restless and did not seem to acquire a mental and physical calmness during this time. November 17, 1941, the patient was operated upon again. Anesthesia was induced with intravenous pentothal sodium in his room. In the operating room 75 mg. of procaine hydrochloride was given intraspinally in the third lumbar interspace. Anesthesia, as determined by pinching the skin with a Backhaus forceps, was obtained to the third intercostal space. Inhalation ethylene anesthesia was then given and a bilateral subtotal thyroidectomy performed.

The patient had a surprisingly smooth operative course. The blood pressure was maintained at about 140/80 and the pulse between 100 and 120. Postoperatively, his condition was good and, except for a hematoma in the wound, his course was uneventful. He was discharged, Nov. 30, 1941, with instructions to report for checkup to the outpatient clinic. When seen Jan. 16, 1942, his basal metabolic rate was plus 35 per cent, his weight was 215 pounds, and he looked and felt well. April 16, 1942, his basal metabolic rate was plus 12 per cent, his weight 220 pounds, and he was doing moderately heavy work.

To date, we have operated upon twenty patients with severe hyperthyroidism, using a combination of intravenous pentothal, spinal and

inhalation anesthesia. Under this regimen we have been able to do bilateral subtotal thyroidectomy upon patients who heretofore we would have done only stage procedures. In eight of the patients the basal metabolic rate was never lower than plus 60 per cent before operation. (See Table I.) We have been impressed with the smooth operative and postoperative course in these cases.

The whole purpose of the spinal anesthesia as used in these cases is to inhibit medullary adrenal releases during the operation, which would forestall the occurrence of an immediate severe postoperative reaction. It is not the intent to secure anesthesia to a level (second to fourth cervical segment) which would permit the operation being done under this agency alone. The question comes up, of course, how do we know that the adrenals are so important in thyroid storm. We believe that the adrenals are important, first because of the reactions accompanying the so-called Goetsch test. In this test, if adrenalin is given intravenously to patients with mild or latent hyperthyroidism the patient gets a reaction akin to a thyroid storm. Second, if there were signs of hyperadrenalin, one would expect an increase in the blood sugar. We have examined the blood sugar of these patients before, during, and after thyroidectomy using spinal anesthesia, and have found that the blood sugar is not increased. The short-time factor in performing the operation must be taken into consideration in evaluating these normal levels. No determinations of the amount of adrenalin in the blood during these operations have been made as there is no accurate method known to date.

It is important that a somatic analgesia to about the fourth dorsal segment be derived from the use of spinal anesthesia, if one hopes to inhibit the splanchnic nerves to the adrenal glands. We have checked the level of spinal anesthesia by noticing when the patient gives evidence of pain by pinching the skin of the chest at different levels before induction with general anesthesia and after operation when the patient is arousing from the anesthetic.

Procaine has been used as a spinal anesthetic, the dose varying from 80 to 120 mg. The head of the table may be tilted downward 10 degrees for a few minutes to assure high enough anesthesia. In so doing, the patient's head should be raised on a pillow to prevent the anesthesia from extending to the cervical segments.

In these cases we have not used any pressor drugs to prevent or treat falling pressure. In two instances the blood pressure fell rather alarmingly during operation. This was treated by Trendelenburg position and intravenous fluid.

It is to be emphasized that it is not necessary to use a spinal anesthetic in all thyrotoxic cases. However, for our experience, its use in the operative treatment of certain cases of severe hyperthyroidism would seem justified and the risk seems less than it would be if one attempted to do the same operation without the spinal anesthetic.

TABLE I

PATIENT	HOSPITAL NO.	AGE (YR.)	SEX	CLINICAL DIAGNOSIS	DURATION OF SYMPTOMS	LENGTH OF PREOPERATIVE TREATMENT	OPERATION	PATIENT'S CONDITION		B.M.R. (%)	PULSE	WEIGHT (LB.)
								DURING OPERATION	AFTER OPERATION			
E. M.	702469	27	F	Diffuse hyperplastic goiter	3 yr.	2 to 3 weeks	Bilateral subtotal thyroidectomy	Good	Good; little rise in blood pressure	(A) *+68 +19 (B) --- (C) + 5 3 mo. P.O	(A) 70 (B) 100 (C) 84	(A) 189 (B) 188 (C) 197½ 3 mo. P.O.
O. K.	728088	32	F	Diffuse hyperplastic goiter	3 mo.	2 weeks	Bilateral subtotal thyroidectomy	Good	Good	(A) +81 +70 +34 (B) --- (C) –10 6 wk. P.O.	(A) 80 (B) 110 (C) 80	(A) 130 (B) 132 (C) 154 6 wk. P.O.
H. S.	728204	27	F	Diffuse hyperplastic goiter	4 mo.	2 weeks	Bilateral subtotal thyroidectomy	Good	Good	(A) +73 +57 (B) --- (C) –11	(A) 90 (B) 120 (C) 100	(A) 140 (B) 140 (C) 155 6 wk. P.O.
E. P.	733570	30	F	Diffuse hyperplastic goiter	3 yr.	10 days in hospital	Bilateral subtotal thyroidectomy	Good	Good	(A) +70 +48 (B) --- (C) + 7	(A) 85 (B) 90 (C) 80	(A) 146 (B) 144 (C) 161½ 9 wk. P.O.
E. L.	736110	20	M	Diffuse hyperplastic goiter	3 mo.	15 days	Bilateral subtotal thyroidectomy	Good	Good	(A) +64 +32 (B) --- (C) Not done; too recent	(A) 100 (B) 90 (C) 90	(A) 120 (B) 122 (C) 124 1 week
A. T.	736054	32	F	Diffuse hyperplastic goiter	9½ mo.	21 days	Bilateral subtotal thyroidectomy	Fair	Good	(A) +92 +51 (B) --- (C) Not done; too recent	(A) 110 (B) 90 (C) 100	(A) 119 (B) 120 (C) 134½ 4 wk. P.O.
S. D.	717339	36	F	Diffuse hyperplastic goiter	7 mo.	2 weeks	Bilateral subtotal thyroidectomy	Good	Good	(A) +62 +62 (B) --- (C) +34	(A) 110 (B) 100 (C) 90	(A) 102 (B) 104 (C) 110 3 wk. P.O.

*(A) Before surgery. (B) After surgery. (C) At discharge or later.

SUMMARY

We have been impressed with the use of spinal anesthesia as an adjunct to the operative and postoperative management of severe hyperthyroidism. The basis of the proposal is predicated on the thesis that an effective spinal anesthesia, which would inhibit medullary adrenal releases during the operation, would help to forestall the occurrence of immediate severe postoperative reactions. It is not the intent to secure anesthesia to a level (second to fourth cervical segment) which would permit the operation being done under this agency alone. On the contrary, a somatic analgesia to about the fourth dorsal segment is derived with the use of spinal anesthesia, the analgesic for the performance of the operation upon the neck being obtained with the use of other agents, usually a combination of pentothal and cyclopropane. The idea is rational and feasible; further investigation is necessary to determine how valid the premises are.

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THE MANAGEMENT OF POSTOPERATIVE COMPLICATIONS IN THYROID SURGERY

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THE early detection and proper management of postoperative complications are an essential part in the care of all surgical cases. In surgery of the thyroid gland, however, immediate and personal attention to postoperative care is not only desirable, but frequently is life-saving. In few other fields of surgery may the postoperative troubles of the patient so quickly produce dire results. It is important, then, in any discussion of thyroid surgery that due attention be paid to postoperative care.

As has been so frequently observed, a set team of anesthetist, surgeon, assistant, and nurse is of the greatest value in thyroid surgery and in postoperative care. The less frequently the personnel of this team is changed the more smoothly and efficiently do they work. In our clinic, the anesthetist accompanies each thyroid patient back to the room and sees the patient safely into bed. She makes certain that the patient's airways are free. If there is any doubt about this, she remains with the patient until breathing is comfortable and easy. Oxygen is given many patients for some hours after operation, especially if they are toxic, and this is started and checked by the anesthetist. Either a tent or an intranasal catheter has proved most satisfactory in our hands. Most patients find the B.L.B. mask unpleasant to wear.

Intravenous fluid is also ordered and frequently given by the anesthetist immediately on the patient's return to bed. This may be glucose in water or glucose in saline solution, with or without Lugol's solution added, as the situation demands.

On return to bed the patient is placed flat or on one side for the first six or ten hours. Then the head of the bed is gradually raised and a sitting position assumed and maintained for most of the immediate postoperative period.

Nausea and vomiting[2, 3] are not infrequent annoyances in the first twelve to twenty-four hours after goiter surgery. Usually due to the preoperative and postoperative medication and the anesthesia, they are readily managed by replacing intravenously the fluids and salts that have been lost. Not infrequently we find that the nausea and vomiting seem to be related to injections of morphine and cease when this

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drug is discontinued. Very often at the end of the first postoperative day codeine and aspirin are substituted for morphine and effectively control discomfort. Except in the rare cases of vomiting due to a postoperative storm, this complication has never been a serious problem.

Postoperative hemorrhage[2, 3, 6, 10, 11] is a very rare occurrence today in thyroid surgery, but when it occurs immediate and active treatment is essential. No serious hemorrhage has occurred in our practice for many years, due, we believe, to our constant attention to all oozing in the field at operation and our tendency to tie both the superior and inferior thyroid arteries in each case in which oozing is troublesome.

Hemorrhage, when it does occur, may develop at catastrophic speed. Usually patients having a serious thyroid hemorrhage suffer more from the resulting pressure of the blood on the trachea than they do from acute blood loss. A patient perfectly comfortable one moment may suddenly develop a wide swelling across the neck which bulges forward almost obliterating the normal submental depression. With this swelling there is increasing stridor and anxiety, and very little time for delay. The skin clips must be removed in the room and the sutures holding the prethyroid muscles cut. This releases the tracheal pressure and overcomes the stridor. Large gauze packs are placed over the wound and the patient is quickly transported to the operating theater for control of the bleeding.

In our experience a severe hemorrhage of this type has always been from the superior or inferior thyroid artery. It has been disconcerting in some of these cases to find no artery pumping when the field was exposed. After careful exploration, however, the vessel usually starts bleeding again and the main trunk can be tied. When no one vessel can be found in such a case, it is best to ligate both superior and inferior thyroid arteries before sending the patient back to bed.

Occasionally a hematoma[7] will appear under the skin flap three or four days postoperatively, the wound having been normal up to this time. No interference with breathing is present. We usually find that this is due to oozing from a small vein under the skin flap. The postoperative course will be shorter and smoother and the scar probably better if this hematoma is evacuated in the operating room and the skin edges reapproximated. Frequently one dislikes subjecting the patient to a second operation and, therefore, waits for the hematoma to liquefy and drain externally. This requires many dressings, but usually the results are good.

For two years or more, we have removed all the skin clips in the thyroid incision twenty-four hours after the operation. This, we believe, has greatly improved the scars. No wounds have separated and no trouble has occurred due to this procedure.

In past years it has been our experience that 85 per cent or more of all our thyroid incisions showed a collection of serum[2, 6] under the skin

flap during the postoperative course. By probing with a small needle this was released with little serious effect on the scar. In recent years, however, serum has been extremely uncommon in these wounds and, in fact, rarely occurs unless a hematoma has been present. This change, we believe, is due to our use of 4-0 catgut for ties in the skin flap, fine catgut in the deep ties, and our technique of retracting rather than cutting the prethyroid muscles in most cases. Less trauma and less catgut have given markedly improved wounds.

Sometimes in large goiters there is a brawny edema[2] extending across the neck for several days postoperatively. This generally clears up in a few days. Any accompanying discomfort is alleviated by hot poultices or ice bags. Very rarely infection[2, 3, 6] occurs under the skin flap. This has never been dangerous. It is treated with hot flaxseed poultices and probing for any purulent fluid in the wound. Anesthesia of the skin flap[2] may persist for some time, but is usually gone at the end of six months.

Very rarely in extremely toxic patients there may be jaundice, probably due to accentuation of the liver damage[7, 10] occurring in severe hyperthyroidism. A high carbohydrate, high protein diet should be given in these cases as well as generous amounts of intravenous glucose.

Infection extending into the superior mediastinum[2, 3, 10] may occur after thyroid surgery, but certainly this is one of the rarest complications in our experience. It is most to be feared following the removal of a deeply substernal goiter. It should be suspected if there are a rising pulse and a moderate fever, the pulse usually being proportionately much higher than the fever or toxicity of the patient. X-ray pictures should show typical widening of the mediastinum. Immediate reoperation to cut transversely the prethyroid muscles and drain the mediastinum is indicated. The prognosis is bad unless the fluid released is the result of inadequate drainage of the substernal area and is relatively sterile. Chemotherapy is used in these cases and may be helpful.

Some degree of tracheal irritation and tracheitis[2, 3, 10, 11] is very common after thyroidectomy. We believe that the degree of tracheitis is in most cases directly proportional to the roughness of the surgery. Rough handling of the larynx and trachea, especially on the posterior surfaces, seems to us to produce marked tracheitis. Certainly the dissection of the thyroid from the front of the trachea causes little difficulty. Mild degrees of tracheitis disappear in from twenty-four to forty-eight hours without special treatment. In some instances a steam kettle in the room seems to make breathing more comfortable.

Marked stridor, cough, trouble in swallowing, and even regurgitation of liquids through the mouth or nose occasionally occur in postoperative goiter cases. These are most unusual, and it is probably true in such cases that there has been an injury to: (1) either the superior or inferior laryngeal nerve, (2) the fine muscles of the larynx or, possibly, as Cole[5]

has suggested, (3) an actual spasm of the tracheal muscles. Temporary relief in these patients may be gained by using oxygen, or oxygen and helium inhalations. If marked swelling is present in the wound it must at once be widely opened and preparations made for tracheotomy.

The surgeon's great tendency in the presence of marked stridor is to delay tracheotomy too long. Men still say that "when cyanosis appears, a tracheotomy must be done." This policy of waiting for cyanosis before doing a tracheotomy will result in some fatalities because the margin of safety in partial tracheol obstruction is very low and any slight increase in the obstruction may at once produce a fatality. We have done tracheotomies in such cases, being gratified by the immediate relief obtained and astonished at the failure of the procedure to leave an unsightly scar.

Certainly we are convinced that marked tracheal obstruction with severe stridor can occur without any injury to the recurrent laryngeal nerves. We have seen both vocal cords functioning well, and normally five days after a tracheotomy had been necessary for tracheal and laryngeal spasm with obstruction.

Injury to one recurrent laryngeal nerve[2, 6, 8] may occur during thyroidectomy with no accompanying symptoms. After the operation the patient's voice may be affected, particularly as to the tone and volume. In many instances the voice returns very nearly to normal, but in others a permanent change is apparent. Injury to one recurrent laryngeal nerve is, in our experience, very rare and never fatal. No special treatment is indicated.

Injury to both recurrent laryngeal nerves is a most serious matter, carrying in its train marked or even fatal postoperative complications. Bilateral injury to the recurrent nerves should be prevented at any cost. In over 5,000 goiter operations performed by one of us (H. M. C.) this has never occurred.

Bilateral vocal cord paralysis may cause immediate and serious laryngeal obstruction with obvious inspiratory stridor. Examination of the larynx makes the diagnosis readily apparent. If the obstruction is pronounced, immediate tracheotomy must be done. In many cases the seriousness of this complication is not apparent until the patient is up and about. With increased exercise, breathing becomes much more difficult and a great increase in stridor occurs.

In these cases it is wise to postpone any radical treatment of the paralyzed cords for eight or ten months or more. Occasionally, one of the cords will regain its motility and the breathing will thereby improve. If, after such a delay, there is still complete bilateral cord paralysis, radical operation for its improvement may be advised.

Hoover[8] has had good results with bilateral submucous resection of the cords in these cases. More recently King[9] has reported good results

from transplanting the omohyoid muscle to the base of one arytenoid cartilage and reconstructing the larynx, thus enlarging the glottic fissure.

Postoperative thyroid storms[2, 10, 11] are today far less frequent and much less severe than in the past. With the increasing care and greater length of the preoperative preparation of thyrotoxic patients and careful adjustment of the stages of operation to each individual, serious thyroid storms can be avoided. From our experience to date with thiouracil,[12, 13] we believe that the few serious reactions we now see after thyroidectomy can probably be avoided.

In recent years the occasional serious reactions after thyroid operations have manifested themselves largely by an undue increase in the pulse rate and a rise in temperature. Formerly these symptoms were commonly accompanied by nausea and vomiting, often very persistent. Rarely today do we see the great muscular activity and mental and emotional excitement that were so frequent in the early days of thyroid surgery. Perhaps this is due to the improved preoperative preparation.

In serious postoperative thyrotoxic cases we place the patient in an oxygen tent at once and continue this for hours or days as is indicated by the patient's reactions. Intravenous instillations of 5 per cent glucose in normal saline solution alternated with 5 per cent glucose in distilled water are given so that the urinary output is brought to 1,000 or 1,500 c.c. per day. Ten minims of Lugol's solution are added to each intravenous infusion until 30 minims per twenty-four hours have been given. Morphine is given in sufficient doses so that the patient rests quietly.

Careful attention must be paid to the lungs in these cases and chemotherapy with the appropriate sulfonamide drug started at once if any suggestion of pneumonia is present.

Following surgery (whether this is directed at the thyroid gland or elsewhere), patients with hyperthyroidism tend to show evidence of increased load on the circulation. The pulse rate quickens and the blood pressure sometimes rises. The systolic pressure rises proportionately more than the diastolic pressure. There are accompanying evidences of hurried circulation. Although there is much individual variation, the average curve of the load on the circulation appears to rise slowly during the first twenty-four hours, then rise abruptly. Then, during the thirty-six to forty-eight hours following the operation there is, typically, a rapid lessening of the load toward normal. In some, the return toward normal is delayed for several days even though there are no apparent complications. During this period when the circulatory load appears to be high, other symptoms of increased hyperthyroidism may appear.

Congestive heart failure rarely appears *for the first time* following operation, although in patients who have had heart failure previously and in the rarer cases in which the patients have to be operated upon

while actually in congestive heart failure, signs of failure may reappear or be somewhat aggravated. Elderly patients and those with other complicating heart conditions should have special care, to spare the heart unnecessary strains. They must have adequate rest, sedation, nursing care, and oxygen, if needed, and in particular they must have their fluid administration carefully controlled so that there is an adequate supply but not an excess. It is easy to overcrowd the circulation and produce signs of congestive heart failure by heedless forcing of fluids to old people or those with a cardiac condition. It sometimes produces violent attacks of paroxysmal dyspnea. For such thyrocardiacs or potential thyrocardiacs, it should be a rule to visit each one frequently, and always before any large amount of fluid is given; routine orders for fluid administration must not be relied upon. A nurse should stand by the patient while intravenous fluid is given, with instructions to stop the administration instantly if respiratory distress or quickened breathing appears.

As is commonly known, hyperthyroidism tends to cause *auricular fibrillation*. It is a "law" that if hyperthyroidism causes auricular fibrillation, when the hyperthyroidism is adequately treated the auricular fibrillation will disappear. Therefore, many patients who have auricular fibrillation when first seen return to normal rhythm when the hyperthyroidism is treated. No treatment directed at the auricular fibrillation is needed except control of the rate by digitalis. A long time should be allowed to go by following surgery before special medication other than digitalis is indicated in an attempt to restore normal rhythm.

Patients who have normal heart rhythm when operated upon frequently develop auricular fibrillation during the postoperative period when the load on the circulation is high. Those who have had transient attacks of auricular fibrillation before operation are most likely to develop it during the critical postoperative period. Among those who have not had it previously, it rarely appears postoperatively in patients under 40 years of age. It appears more and more often as age advances. The severity of the hyperthyroidism and the postoperative reaction are also factors.

The appearance of auricular fibrillation in a patient following thyroid surgery is not cause for alarm. Nor does it indicate drastic therapeutic efforts. It does indicate watchfulness, close attention to the patient's wants and comfort, and thoughtful treatment with digitalis or drugs with similar action. For years we have used digitalis in the control of the rate in auricular fibrillation in hyperthyroidism with gratifying effect. Our rules for its use are as follows: We do not use digitalis in patients who have normal rhythm. Rare exceptions to this rule would be (1) patients with complicating serious heart disease, and we sometimes digitalize carefully (2) patients who have had re-

peated attacks of transient auricular fibrillation, since they are almost certain to have a return of the auricular fibrillation postoperatively, and we can anticipate this comfortably by leisurely digitalization in preparation for operation.

Some variations in the strength of digitalis preparation are to be expected, and some variation in the tolerance of individuals to the drug. Slight over digitalization, if not long-continued or severe, is usually not actually dangerous. But it can cause distressing and even serious symptoms. At best, it is uncomfortable for the patient.

Until recently, we have given from one-half to two-thirds of the estimated full dosage at the first dose, and then three-grain or one and one-half grain doses every eight hours until the heart rate is satisfactorily controlled or until toxic symptoms appear. We then maintain the action by suitable daily doses under supervision.

This plan has worked well, but by this method there is usually a delay of many hours before the patient's circulation has received the full benefit of the drug action. Recently we have used a preparation of Lanatoside C, intravenously. We have used for the initial dose approximately 6.5 cat units. There may be a prompt and appreciable response. On several occasions normal rhythm has appeared within less than one-half hour after the first intravenous dose, but often considerably more has been needed, either intravenously or by mouth or rectum, before the pulse rate has been satisfactorily controlled. We are still learning about the amount and timing of the dosages, and therefore do not recommend any fixed procedure. But we believe that the intravenous use of Lanatoside C is a distinct advance in the treatment of auricular fibrillation when it first appears, and when the patient has not had digitalis within two weeks.

Auricular flutter occasionally occurs postoperatively and is regarded and treated like auricular fibrillation. Other paroxysmal tachycardias are no more likely to occur after thyroid than after other operations.

Since hyperthyroidism and myxedema rarely if ever appear as immediate postoperative complications in thyroid cases, they are not discussed in this paper.

Tetany[2, 6, 7, 10, 11] occurs after thyroid surgery if the blood supply of the parathyroids is partly destroyed or if a sufficient number of parathyroid glands are removed to reduce markedly their secretion. Postoperative tetany is rare and is usually transient. We have seen one transient case in our last 1,000 thyroidectomies.

Tetany may be suspected if typical carpopedal spasms and other muscular contractions occur hours or days after a thyroidectomy. Trousseau's and Chvostek's signs when positive make the diagnosis quite certain. Examination of the blood calcium will show it to be low. Occasionally postoperative tetany will have a sudden onset and the patient will have such muscular spasms that breathing and swallowing

are rapidly and seriously affected. Here there is no time for blood calcium studies. Active measures must be undertaken at once.

In such acute cases from 5 to 10 c.c. of 10 per cent calcium chloride should be given at once intravenously, mixed with 100 c.c. of normal saline solution to prevent sloughing. This is effective in a matter of minutes and controls the acute spasms. Calcium lactate, from 2.5 to 4 Gm. dissolved in hot water, every two to four hours along with two to three teaspoons of cod-liver oil daily assists the calcium metabolism. Calcium lactate, being less irritant, is sometimes given intravenously instead of calcium chloride and requires no saline solution for dilution. Occasionally parathormone extract subcutaneously may be used. Pemberton and Stalker[11] feel that A.T.10 with calcium lactate may be the easiest way to treat chronic parathyroid deficiency. All such therapy must be carefully followed and repeated blood calcium studies made.

Severe ocular complications[10] may follow thyroid surgery in patients having marked exophthalmos. These may be due to injury to the cornea during the adjustment of the anesthetist's mask, or other types of trauma and infection in eyes left unprotected by incomplete closure of lids. Such eye complications should be seen and treated at once by an ophthalmologist. The thyroid surgeon and his team must be particularly careful before, during, and after operation, in the care of the eyes of the patients who have pronounced exophthalmos.

The scar[2] after a successful thyroidectomy is usually the only reminder that the patient has of her previous illness. In a few months all the symptoms that made thyroid surgery necessary will be forgotten, but the scar, especially if it is a bad one, will remain and will receive much attention; hence we lay great stress on the proper placing of the thyroid incision at operation and its care afterward. As previously stated, we remove all the clips twenty-four hours after the operation; superficial drains are removed with the clips; if serum or blood collects under the skin flap it is immediately released by use of a very fine probe. When the wound is healed there may be adherence between the scar and the fascia which causes an unsightly irregularity. This can be improved greatly by gentle massaging to lengthen the adhesion. We start this ten or twelve days after operation. Deep induration and swelling may be present for five or six weeks in some cases, especially if the muscles have been cut. No treatment for this other than reassurance is needed.

It is apparent that with adequate preoperative preparation of the toxic thyroid patient the most serious complication of thyroid surgery, postoperative storm, will be absent or mild. It is equally true that with increased technical skill the difficulties due to injury of recurrent laryngeal nerves or to parathyroid glands can be avoided. Today the complications after thyroidectomy are chiefly those common to any operation, and like all surgical complications can be largely avoided by careful preparation for operation and a skillful operative technique.

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THE PROBLEM OF THYROID CRISIS*

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DESPITE the great progress made in the last several decades in the recognition, treatment, and pre- and postoperative care of patients with diseases of the thyroid gland, there is still that group of patients who suddenly and unexplainedly, during the course of their disease, showed a profound and severe reaction designated as thyroid crisis. This interlude in the course of an apparently well-known disease is the cause of much speculation and the source of much medical comment.

As in all diseases resulting from a malfunctioning of the glands of internal secretion, there are all degrees of apparent dysfunction of the thyroid gland. Those patients exhibiting a marked disturbance of the central nervous system with overwhelming changes in the heat-regulating mechanism and accentuation of all of the symptoms of thyrotoxicosis are adjudged in thyroid crisis. To many clinicians any sudden pre- or postoperative variation in this direction is termed crisis, while to others only those patients who progress and terminate fatally fall into this group.

A wide clinical, pathologic, and physiologic search of the nervous system, the cardiovascular system, the liver, thymus, and adrenals, along with the physicochemical analysis of certain elements in the circulating body fluids in these patients has failed, to date, to shed any clear light upon a single factor to which the etiology of thyroid crisis can be solely attributed. Much of the recent experimental work has been carried out on this problem, and many of the clinical manifestations of the patient in crisis reproduced and an explanation tendered.

In an overall survey of the frequently reported cases, two outstanding clinical features appear common to all: (1) There is a progressive augmentation of all of the symptoms of thyrotoxicosis as it pertains to each of the great body systems (central nervous system, cardiovascular system, and hepatorenal system) until recovery or death ensues. (2) The terminal clinical signs and symptoms and the necropsy findings emphasize a breakdown in one or more of these systems. There is no uniformity of findings and no pathognomonic features common to all cases.

It is our impression that thyrotoxicosis is not a fatal disease when correctly treated, that thyroid crisis is not a specific entity, and that death in this state results from the various complications associated with the augmented metabolism which are often injudiciously and inaccurately treated.

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The deaths in thyroid crisis are frequently "cardiac deaths," at least terminally, and this aspect has received universal attention. There are at least three opinions concerning the effects of thyroid disease on the heart,[1] namely, (1) that thyrotoxicosis has no effect upon the heart except to increase the metabolic activity, (2) that the thyroid disease causes myocardial damage, hypertrophy of the heart, and various clinical cardiac manifestations, and (3) that thyrotoxicosis acts only as a catalytic agent and brings to the surface latent cardiovascular lesions.

The work of Raab[2] and of others suggests, as a fourth alternative, that increased production of epinephrine-like substances may produce the myocardial hypertrophy and dilatation, the arrhythmias and the myocardial degeneration in patients with thyrotoxicosis. He has found abnormally high concentrations of "epinephrine-like catechols" or of epinephrine proper and sympathin in the hearts of the majority of a selected group of patients who died from cardiac failure. Certain horhormonal and nutritional factors were found to enhance the accumulation of the epinephrine-like catechols in the hearts of experimental animals. Two of these factors which qualitatively increased this desired accumulation were an overdose of thyroxin and a vitamin B_1 deficiency. The fundamental role of sympathomimetic amines with a catechol nucleus in the generation of myocardial disease is further stressed by an abundance of observations regarding the experimental production of the characteristics of myocardial disease (arrhythmia, anoxic changes in the electrocardiogram, anginal pain, pulmonary edema, hypertrophy and dilatation of the heart, myocardial degeneration and necrosis, cardiac failure and death) through the administration of epinephrine and related amines.

Crile[3] has pointed out that the known precipitating factors of thyroid disease (fear, anger, worry, infections, operations, pain, asphyxia, hemorrhage, and physical exertion) are factors stimulating the adrenals.

With some of these facts in mind Maddock and associates[4] studied the concentration of epinephrine-like substances in the blood of patients with hyperthyroidism. No evidence was found of this substance in the peripheral venous blood of the majority of the patients who were responding well to the routine preoperative treatment. In patients whose progress was not satisfactory and in whom fever was present, the test occasionally showed the presence of a small amount of epinephrine-like substance. A few patients postoperatively showed a positive test, the highest values being obtained in two patients of the group tested who developed severe thyroid crisis. In one of these, the patient who recovered, the epinephrine test became negative about the time the crisis subsided.

After correlation of these facts and findings, one may assume that the clinical cardiac findings and the cardiac deaths resulting in thyrotoxicosis and thyroid crisis follow excessive concentration of the sympa-

thomimetic amines in cardiac muscle. The effect of the sympathomimetic amines upon the oxygen uptake in cardiac muscle and therefore the effect of diminished oxygen pressures or anoxia is not well known.

Perhaps the most outstanding features, and certainly the most striking in thyroid crisis, are those of the central nervous system. They are in general the symptoms produced by an anoxic anoxia. In milder cases of thyroid crisis, patients have the general features of "mountain sickness," a feeling of well-being, exhilaration, talkativeness, emotional outbursts (such as laughing and crying), quarrelsomeness, and development of fixed ideas. The symptoms of fulminating crisis are those of a severe, acute oxygen deprivation, namely, delirium, mania, hyperpyrexia, and coma.

Since Magnus-Levy, in 1896, suggested that the thyroid hormone might act either directly on tissues or indirectly by way of the nervous system, numerous attempts have been made to locate its site and manner of action. An outstanding contribution to this problem was made by Cohen and Gerard[6] in 1937. These workers and others have shown in experimental animals that the respiration of individual cells is enhanced by thyroid hormonal action, for an increased oxygen consumption by hyperthyroid tissues persists in vitro. The oxygen consumption of hyperthyroid brains is approximately four times as much as that of normal brains on adding substrates which are involved in carbohydrate oxidation and glycolysis. Analysis of the respiration changes, induced by accelerators, methylene blue and cresyl blue, and such inhibitors as cyanide, malonate, iodoacetate, arsenite, barbital, and urethane, indicates that the absolute concentration of various enzyme systems is greater in hyperthyroid than in normal brain and that certain dehydrogenases are increased relatively more than oxidases. This work has been further investigated by Kessler and Gellhorn,[7] who found the sensitivity of unanesthetized animals to lowered oxygen pressure was greatly accentuated following the administration of thyroid powder. The electroencephalogram was the method used to record these results.

One may conclude from these statements that many of the abnormal manifestations in the central nervous system seen in crisis are the results of anoxia and follow the presence of excessive amounts of circulating thyroid hormone. It has long been known that the effect of administered synthetic thyroxine develops slowly (about seven hours) and lasts for a long time (five to six weeks).[15] The usual manifestations seen postoperatively may well not reach their maximum effect for from eight to ten days.

The profound and striking disturbances in the heat-regulating mechanism in thyrotoxicosis and thyroid crisis have evoked little experimental observation. It is known that the stimulation of the autonomic centers by artificial fevers produced with typhoid vaccines results from the stimulation of the sympatheticoadrenal system in the normal and vagotomized experimental animal.[8] The clinical and experimental stud-

ies carried out by Goetsch and Ritzmann[9] indicate that the hyperthermia is due to the action of epinephrine, whose effect is apparently enhanced in hyperthyroidism.

Jaundice has been noted and recorded on many occasions as a complication of thyrotoxicosis and particularly of thyroid crisis. Many studies have been carried out to determine whether there is any relationship between liver damage and the production of thyroid crisis, particularly that which has occurred postoperatively. No definite, consistent relationship has been noted and no prognostic evidence is forthcoming to date. Regardless of these facts the occasional patient shows profound evidence of liver damage in the course of his disease. In a few instances the clinical picture has apparently warranted a diagnosis of acute yellow atrophy. The most consistent change in the function of livers in patients with hyperthyroidism is their inability to store glycogen and to convert levulose in large amounts to dextrose. With prolonged thyroid feeding experimentally there is a profound decrease in liver, muscle, and heart glycogen. At this stage liver glycogen is easily mobilizable.

One might be tempted to ask whether epinephrine has anything to do with the liver damage seen in thyrotoxicosis; Perazzo's[10] work suggests that it has. He found well-advanced fatty degeneration of the liver with moderate doses of the drug.

The pathologic findings in the liver of patients dying with clinical and pathologic evidence of hyperthyroidism have been reported by many authors. There is some lack of universal agreement in the uniform location of the histopathologic changes. All are in agreement that the changes are neither pathognomonic nor of clear prognostic import. Weller[11] describes a patchy parenchymatous interlobular hepatitis. Beaver and Pemberton[12] distinguish three predominant types of lesions in exophthalmic goiter: (1) Acute degenerative lesions (fatty metamorphosis, focal and central necrosis, and changes secondary to stasis of blood); (2) simple atrophy; and (3) subacute toxic atrophy and toxic cirrhosis. The lesions described in the third classification appear among older patients, in whom the disease is of longer duration and of more than the average severity. Lord and Andrus[13] have more recently outlined the liver findings in their series of patients with thyrotoxicosis. They likewise describe three characteristic changes common to all patients: (1) Large droplets of fat diffusely distributed in the parenchymal cells; (2) central necrosis of the hepatic cords with marked infiltration of the necrotic areas by polymorphonuclears and erythrocytes, and (3) connective tissue proliferation in the portal areas with an infiltration of lymphocytes. McIver and Winter[14] have studied the deleterious effects of anoxia on the livers of experimental animals made hyperthyroid by the injection of crystalline thyroxin. Their animals were then subjected to periods of reduced oxygen concentration. The histopathologic picture of these animals shows extensive necrosis of the

liver cells about the central areas with some inflammatory cell infiltration in the portal areas. The earliest changes consisted of fatty metamorphosis and engorgement of the blood vessels in the central areas.

The liver changes just described can be produced by anoxia of an anoxic type in experimental animals in apparent hyperthyroid states; the correlation may be more than fortuitous. At present it would seem to us that the hepatic changes appearing in patients with hyperthyroidism and in thyroid crisis may well be explained on a basis of chronic anoxia in an organ already showing an increased oxygen consumption and glycogen depletion. There is at this time no substantial proof that the thyroid hormone in either exophthalmic or adenomatous goiter contains a direct cytotoxic element.

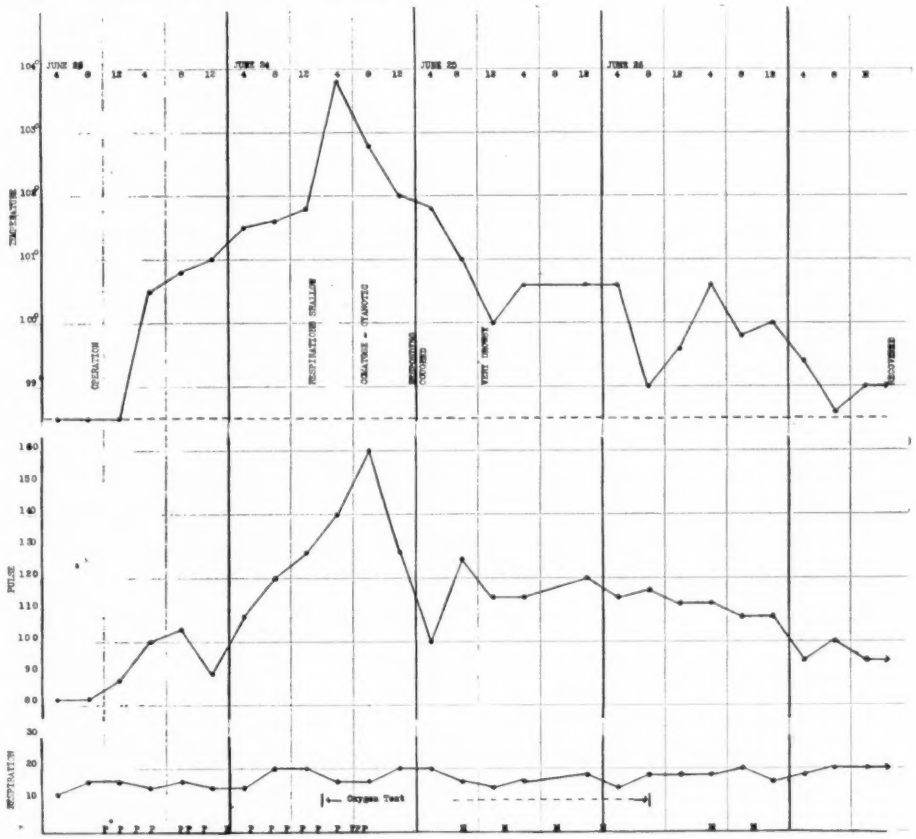
On the assumption that the opinions and facts as stated here are correct, an attempt has been made to correlate these with the findings on patients upon whom a diagnosis of thyroid crisis has been made. A small series of consecutive patients, seen over a period extending between the years 1934 to 1943 on the medical and surgical services of the University of Michigan Hospital, has been reviewed. Well over one-half of these patients died in "thyroid crisis." The greater portion of them were between the ages of 40 to 70 years. A toxic adenomatous goiter was seen in a ratio of 2:1 over the Graves' constitution thyroid. Close inspection of the records of these patients and the clinical findings present during the stage of crisis along with the available necropsy findings in those patients who died revealed that in every instance one or more factors were present to which the immediate cause of the profound symptoms and of death could be well attributed. A list of these factors includes diabetes mellitus with coma, pulmonary edema and congestion, atelectasis, hepatitis and cirrhosis, wound infection, oversedation, cardiac failure, pneumonia, septicemia, and overdigitalization. Bayley[15] and Ransom and Bayley[16] have made an analytic study of the pre- and postoperative fatalities due to thyroid crisis. Both authors emphasize certain factors in the prevention of crisis with the hope of avoiding them in the future.

The precipitating factors in preoperative crisis as summarized by them are as follows:

1. Delay in admitting toxic patients to the hospital
2. Surgical proceedings not directed at control of hyperthyroidism
3. Infections of a wide variety
4. Various minor diagnoses and therapeutic procedures
5. Inadequate sedation

We are in agreement with these conclusions. Infections, minor diagnostic and therapeutic procedures, and injudicious surgical procedures not directed at the control of an existing hyperthyroidism may undoubtedly enhance the oxygen needs of critical tissues as well as

precipitate a profound stimulation of the sympatheticoadrenal system. The role which these factors play in hyperthyroidism has been discussed. Bayley[15] in his study was greatly impressed by that group of patients in whom insomnia appeared to play a critical role in the production of crisis. His statement that "the value of sleep could not have been appreciated sufficiently in some of these older cases" is well taken. However, we are not in complete accord with his suggested choice of medication in the control of insomnia.



*P, Pantopon, gr. ⅓.
M, Morphine sulfate, gr. ¼.

Fig. 1.—Oversedation in the postoperative period after thyroidectomy.

The most striking and outstanding cases in our series were those in which oversedation of the patient played a predominant part in the production of the signs and symptoms. In two patients a proved drug sensitivity was present. In each of the patients there was a prompt, rising crescendo of all of the symptoms of crisis as large, frequent doses of sedatives and hypnotics were given. With increasing symptoms the frequency of drug administration, and often the amount, was stepped up, followed by a further increase in symptoms—a vicious cycle. Prompt improvement seemed apparent with diminution or cessation of these drugs (Fig. 1).

This course appears logical since there is still present in the minds of many physicians the adage that hypnotics, particularly those of the morphine group, should be given "at frequent intervals and by the clock" in postoperative thyrotoxicosis. It is obvious that with the marked depression of respirations occurring as a result of large, frequent administrations of drugs of this series that anoxia may become an important, often critical, factor in the progress of the patient's disease. For this reason we have limited the use of such medications in patients of this group to that necessary to control pain, only, in the postoperative period.

In those patients in whom oversedation did not appear to play a dominant part, other causes of diminished oxygen intake were apparent. These were pulmonary congestion and acute pulmonary edema, atelectasis, pneumonia, cardiac failure, and overdigitalization.

Three patients in this series showed evidence of hepatic damage on post-mortem examination. No patient developed clinical jaundice during the course of his disease. In two patients a "patchy interlobular hepatitis" was present and in the third an early atrophic cirrhosis existed. In none of these patients was there clinical evidence of hepatic disease nor did the liver changes appear to contribute to the cause of death.

The one patient admitted in coma with diabetes mellitus died within a few hours after admission to the hospital. Her blood sugar level just before death measured 540 mg. per cent.

Obviously the patients with severe wound infection and with septicemia were erroneously classified as thyroid crisis.

SUMMARY

In a discussion of the outstanding, climactic aspects of thyroid crisis, we have outlined the chemicophysiologic aspects of the major symptoms and signs as interpreted on a basis of our present-day knowledge of hyperthyroidism. As yet an ultimate explanation of the exact method by which the circulating thyroid hormone brings about these changes described is not forthcoming.

It is our belief that there are all gradations of response to increased amounts of circulating thyroid hormone and that thyroid crisis is an extreme response, differing only quantitatively from reactions of lesser degree and initiated or augmented and often brought to a fatal outcome by intercurrent complicating factors.

A small series of cases were reviewed from this standpoint. We feel that this group, although small, confirms our contention that the profound symptom complex designated as thyroid crisis supervenes only in those patients in whom there is a break in the chemical and physiologic compensatory processes of the individual. The factors involved in this breakdown are listed as they occurred in the patients of our series.

We are also impressed that often the physician, unless conversant with the physiologic responses of an individual to hyperthyroidism, may injudiciously employ therapeutic measures definitely detrimental to the patient.

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GOITER IN CHILDREN

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GOITER in children differs sufficiently from goiter in adults to warrant some special study, particularly since goiter in children is unusual and experience in its management is limited. From reports in the literature[1, 2, 3] it would seem that there is disagreement as to whether the treatment of hyperthyroidism of children should be medical or surgical. Surgeons do not agree as to the amount of thyroid tissue that should be left behind at the time of thyroidectomy and the frequency with which carcinoma is encountered in nodular goiters of children is not fully appreciated.

With these and other differences in mind, a review of the cases of goiter in which the patients were children 14 years of age or less, encountered at the Mayo Clinic from 1908 through 1943, was undertaken and the results form the basis for this report. With the exception of adenomatous goiter with hyperthyroidism, which has not been encountered in children at the clinic, all of the major diseases of the thyroid gland which affect adults have been seen in children. Because of the number of cases involved, the report will be largely concerned with exophthalmic goiter, adenomatous goiter without hyperthyroidism, and carcinoma of the thyroid gland. The series includes 189 cases of exophthalmic goiter, 70 cases of adenomatous goiter, 18 cases of carcinoma of the thyroid gland, and 3 cases of thyroiditis.*

EXOPHTHALMIC GOITER

Although exophthalmic goiter is the disease of the thyroid gland that is of commonest occurrence among children, patients 14 years of age or less with exophthalmic goiter constitute a small proportion of all patients suffering from this disease. Thus, at the clinic, from 1908 to 1943, inclusive, exophthalmic goiter was encountered in only 189 children. Furthermore, although the disease may have its onset even in infancy, it is distinctly rare before the age of 9 or 10 years and more than 80 per cent of children with exophthalmic goiter seen at the clinic were between 10 and 14 years of age. In children, as in adults, more females than males have the disease. The ratio of females to males in the group was 5.9:1.

The clinical picture of exophthalmic goiter in children is essentially the same as that seen in adults, with the exception that late results of the untreated disease are seen far less frequently than in adults. For

*Prior to 1917, the ages of patients with goiter who were not operated on were not indexed. Because of this, children with nodular goiters seen at the clinic from 1908 to 1917, who were not operated on, could not be included in the study.

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the most part, the patients were seen at the clinic after the symptoms had persisted for less than one year, but the duration of symptoms in many cases was much longer. Helmholz[4] reported that nervousness was the most frequent complaint, followed by goiter, tachycardia, and exophthalmos in this order. Tachycardia was present in all cases, goiter in all but 2, nervousness in all but 2, and exophthalmos in 25 of the 30 cases in his series. He concluded that in children nervousness associated with goiter was very suggestive of the diagnosis of exophthalmic goiter. The findings in relation to symptoms in Dinsmore's[5] series of 57 cases were similar to those reported by Helmholz. Nervousness or goiter was the first symptom noted by the patient or his parents in 70 per cent of Dinsmore's cases and tachycardia was found in all. Less reliance can be placed on the basal metabolic rates of children than of adults; first, because of apprehension on the part of the children and, second, because the standards for children would seem to be less dependable than those for adults. Of considerable aid in the diagnosis of exophthalmic goiter in children, as in adults, is the characteristic response to administration of iodine.

Evaluation of the intensity of the disease in children is less exact than in adults and, as a rule, children suffering from exophthalmic goiter have a more severe disease than would be expected clinically. Experience has amply demonstrated that reactions to surgical measures, both at the time of operation and postoperatively, are likely to be surprisingly marked and, because of this, there is general agreement that thyroidectomy should be carried out in stages more frequently in children than in adults. However, judging from the more recent cases in the present series, it would seem that, with adequate preoperative preparation with iodine, the thyroidectomy usually can be done in one stage. Thus, the thyroidectomy was done at one sitting in 16 of the last 18 patients in whom treatment has been carried out at the clinic, and in two stages, approximately three months apart, in the remaining 2. Children should be given iodine in preparation for thyroidectomy for a materially longer period than is necessary for adults. Generally, although adults may be adequately prepared for operation by receiving iodine for approximately ten days, children will require a period of at least three weeks on iodine before operation.

Choice and Details of Treatment.—Although we believe that exophthalmic goiter in children is essentially the same disease as exophthalmic goiter in adults and that treatment in children, as in adults, should be subtotal thyroidectomy, it would seem that medical management by means of iodine and rest may be rarely employed, particularly in children with a mild form of the disease. Of 171 children with exophthalmic goiter seen at the clinic from 1908 to 1940, inclusive, Kennedy[6] was able to secure reports on the late results of treatment of 163, and of these 171, 25 had not been operated on at the clinic for various reasons. Seven of the 25 patients were subsequently

operated on elsewhere and 4 patients had died, not necessarily of hyperthyroidism. Of the 14 remaining patients, Kennedy considered the results of medical treatment to be good in 10, fair in 3, and poor in 1. Since the time of Kennedy's report, 18 children with exophthalmic goiter have been seen at the clinic and in every case thyroidectomy has been performed.

In spite of the obvious technical difficulties of thyroidectomy in very young children, and in spite of the increased tendency of children to react severely following surgical operation, the hospital mortality rate in the present series compares favorably with that following operations on adults. In all, 164 children with exophthalmic goiter were operated on at the Mayo Clinic from 1908 to 1943, inclusive, with 8 deaths, giving an over-all mortality rate of 4.9 per cent. Among 55 children operated on prior to 1922, there were 5 deaths in the hospital, which would suggest that, prior to the days of iodine preparation of patients for surgical operation, the risk to children was far greater than that to adults. However, with adequate preoperative preparation with iodine, the hospital mortality rate after thyroidectomy in children compares favorably with that of adults. Since 1921, then, 109 children have been operated on at the clinic for exophthalmic goiter with 3 deaths, or a hospital mortality rate of 2.8 per cent.

There is disagreement in published reports as to the amount of thyroid tissue that should be saved in carrying out subtotal thyroidectomy in children. Cattell,[7] Dinsmore,[5] Abbott,[8] and others[9, 10] expressed the belief that proportionately more thyroid tissue should be preserved in children than in adults and they emphasized the frequency and seriousness of myxedema following thyroidectomy in children. Welti,[11] and Nixon,[12] who quoted Means, conversely stressed the frequency of persistent hyperthyroidism and the high recurrence rate following thyroidectomy in children; they favored thyroidectomy at least as radical as that carried out in adults. In our opinion, the same relative amount of thyroid tissue should be preserved in children as in adults; and, in the present series, the thyroidectomies in children were for the most part neither more nor less radical than those done in adult patients. Following such thyroidectomies both recurrence and myxedema are not uncommon, but we do not believe the results of thyroidectomy would be bettered if greater or smaller remnants of thyroid were preserved.

Late Results.—It is evident, from the diversity of opinion as to the amount of thyroid tissue that should be preserved at operation for exophthalmic goiter in children, that the results in relation to myxedema and recurrence are not entirely satisfactory. However, in general, the late results in children are good and the great majority of children with exophthalmic goiter remain well following thyroidectomy. Kennedy[6] recently has reported the results following thyroidectomy in children with exophthalmic goiter, 14 years of age or less, seen at the clinic from 1908 to 1940, inclusive. Of the 130 patients who recovered from

operation and concerning whom reports were received, there were 4 late deaths from hyperthyroidism; in 12 cases recurrences had developed, for which 17 operations had been performed, and in 19 cases low basal metabolic rates or frank myxedema had developed. Eighteen other children with exophthalmic goiter have been operated on at the clinic since Kennedy's report, and in 1 patient of this group recurrent exophthalmic goiter has developed but so far has been successfully controlled with iodine; in 6 patients frank myxedema has developed. Follow-up in this group of 18 patients has not been continued for longer than four years.

The results following operations performed since the introduction of medication with iodine have been materially better than those of the time before iodine was used. In the group of 46 patients operated on prior to 1922, and concerning whom follow-up data are available, there were 6 recurrences, 3 late deaths from hyperthyroidism and 2 with myxedema or low basal metabolic rates. Of the 102 patients subjected to operation since 1921, and concerning whom follow-up data are available, 7 have had recurrences, 1 has died of hyperthyroidism, and 23 have developed myxedema or low basal metabolic rates. Four of the patients who had recurrences were operated on between 1922 and 1924, the fifth patient was treated in 1926, the sixth in 1930, and the last in 1939. The recurrence in this case was well controlled by means of iodine in 1943. We do not regard the development of a low basal metabolic rate or of myxedema following operation as serious as the necessity for a second operation because of recurrent exophthalmic goiter. We believe that because of the frequency of myxedema in children following operations on the thyroid gland, and because of the seriousness of unrecognized myxedema in children, they should be examined very carefully two or three months after thyroidectomy, and at subsequent intervals, so that myxedema can be adequately treated with desiccated thyroid before the child has suffered in any way.

ADENOMATOUS GOITER

Adenomatous goiter in children is more unusual than exophthalmic goiter in the same age group. From 1917 through 1943 only 52 cases of adenomatous goiter in which the patients were 14 years of age or less were seen at the clinic, and in none of these cases was the basal metabolic rate significantly elevated. As both Helmholz[4] and Kennedy[13] have pointed out previously, adenomatous goiter with hyperthyroidism has not been encountered in children at the clinic so that, in our experience, hyperthyroidism in children is synonymous with exophthalmic goiter. The adenomas varied in size and number, and the same pathologic variation as in adults was found in the appearance of the adenomatous tissue. The patients with adenomatous goiter ranged from newborn infants to children 14 years of age with the greatest number of patients falling in the older age groups. Nodular enlargement of the thyroid, presumably

adenomatous goiter, has been observed at the clinic in two newborn infants. As with other varieties of goiter, females were affected more frequently than males, the ratio in this group of patients being 2.7:1. Thirty-eight patients were treated by administration of iodine, of desiccated thyroid, or both, given either together or in alternate courses. Kennedy[13] concluded from his study of the same series of cases that the results of treatment were variable in that in some patients the goiter became smaller while in others the size remained unchanged. Enlargement of an adenoma during treatment was not observed. In those cases in which definite adenomatous enlargement persisted it was felt that subsequent surgical removal probably would become necessary.

Surgical treatment, either enucleation of the adenoma, lobectomy, or subtotal thyroidectomy was carried out in 14 patients. There were no deaths in the series. In 2 patients the basal metabolic rate postoperatively was so low that desiccated thyroid was administered, although sufficient time was not allowed to elapse in either case for the possible development of the clinical signs of myxedema.

Apart from the obvious indications for surgical treatment which have to do with the size of the goiter and its mechanical effects on surrounding structures, the possibility of malignancy is often the most important indication for exploration of a nodular goiter in an infant or child. From 1908 through 1943, of the patients 14 years of age or less, 53 with nodular goiter were operated on at the clinic.* Of these, 32 were found to have adenomas, in 3 the nodularity was due to thyroiditis, and the remaining patients, 18 in all, had carcinomas of the thyroid gland. Stated differently, 1 of 3 nodular goiters in patients in this age group that have been explored surgically have proved to be carcinomas. It should be pointed out that in many of these cases a correct preoperative diagnosis was made, but in many other cases, as in adults, the presence or absence of malignancy was determined with certainty only at the time of operation.

CARCINOMA

Eighteen patients 14 years of age or less, with carcinoma of the thyroid gland, were seen at the Mayo Clinic from 1908 through 1943. Kennedy[13] reported that only 6 cases of carcinoma of the thyroid gland had been reported in the American literature during the twenty years prior to 1935 and he estimated that approximately 1 per cent of carcinomas of the thyroid gland occurred in children. One of us (Pemberton[14]) found that of a series of 774 proved cases of carcinoma of the thyroid gland, 17 of the patients were less than 20 years of age, and 4 patients were less than 10 years of age. In each of the 18 cases in the present series the diagnosis was confirmed histologically from study either of the resected specimen or of tissue removed for biopsy. In 2 cases, the specimen for biopsy was removed elsewhere but the tissue was examined here at the time that the patient was examined clinically. Carcinoma

*See footnote page 756.

of the thyroid gland occurs about twice as often in females as in males, while in this series in children 15 patients were females and 3 were males. The age at which symptoms were first noted varied from 12 years to that of a newborn infant. The interval between the onset of symptoms and treatment varied from 4 months to 10 years, and in 12 of the 18 cases two years or more had elapsed between the appearance of the first symptoms and treatment.

Enlargement of the thyroid gland or of cervical lymph nodes was in every case the first sign of carcinoma of the thyroid. In 5 cases the enlarged cervical nodes were far more obvious than enlargement of the thyroid, which in some cases was so little evident that it was not noted in the clinical record. When a mass was present in the thyroid gland it usually was described as hard and irregular, and involved only a portion of the thyroid. In more advanced cases, as in adults, fixation to surrounding structures had occurred and symptoms of hoarseness and dyspnea were occasionally present. In only 1 case were extensive systemic effects present when the patient was first seen. Progressive enlargement of the tumor in the thyroid was noted in several cases but sudden enlargement of a pre-existing mass in the thyroid was noted rarely.

The tissue diagnosis was papillary adenocarcinoma, grade 1 in 12 cases; adenocarcinoma, grade 2 in 2 cases; adenocarcinoma, grade 4 in 1 case; papillary adenocarcinoma, grade 2 in 1 case; and adenocarcinoma, grade 1 in 2 cases. The malignant tissue was noted to be in a fetal adenoma in 1 case of papillary adenocarcinoma and in 1 case of adenocarcinoma, grade 1. Metastasis had developed at the time when the patient was first seen in 11 cases and cervical lymph nodes were involved in all of these cases. In addition, 2 patients had pulmonary metastatic growths at the first visit and in 2 other patients, later, pulmonary metastasis developed. The patient with the adenocarcinoma, grade 4 had metastatic involvement of the calvarium and spinal column when first seen at the clinic.

In 10 cases the lesion was considered operable in that it was possible to resect the involved tissue, but in the remaining 8, the disease was judged inoperable and biopsy only was done. In 2 of these cases the biopsy was carried out elsewhere. In 16 patients irradiation therapy was carried out here and in 1 case such therapy was carried out elsewhere, while the remaining patient died soon after surgical operation and before further treatment could be instituted. The results of treatment depended largely on the extent of the malignancy, but as with carcinomas of low grade of malignancy affecting the thyroid gland in adults, the time of survival after even palliative operations, combined with adequate irradiation therapy, was often surprisingly long.

THYROIDITIS

There were 3 cases of thyroiditis in the series and in each case the question of possible malignancy was raised clinically. One patient, a

boy 12 years of age, had a diffusely enlarged but somewhat nodular thyroid. His basal metabolic rate was –19 per cent but there were no signs of myxedema. He was treated with iodine and desiccated thyroid. In this case the diagnosis was not proved. The other 2 patients were treated surgically. The thyroid of a boy of 13 years was firm, nodular, and slightly tender. The basal metabolic rate was –6 per cent. Subtotal thyroidectomy was carried out and, following the operation, the basal metabolic rate was –14 per cent. There were no signs of myxedema. The last patient, a girl of 13 years, had a firm, nodular thyroid with a basal metabolic rate of –13 per cent. Subtotal thyroidectomy was carried out.

ADOLESCENT GOITER

It is difficult to make any statement concerning the incidence of adolescent goiter in children, because different observers do not agree as to what constitutes an abnormal enlargement of the thyroid gland. It would seem that diffuse, symmetrical enlargement of the thyroid gland is rarely seen at the clinic in children 14 years of age or less and that the condition is very unusual prior to the onset of puberty. In most patients seen at the clinic, when a frank goiter was encountered in this age group, the condition was treated with iodine, desiccated thyroid, or both. In some, after such treatment had been instituted, the diffuse enlargement of the thyroid gland was reduced so that adenomas became palpable. Such cases have been considered under the heading of adenomatous goiters. In the very early years covered by the study, several patients with large, adolescent goiters were operated on, but such patients have not been encountered at the clinic for many years.

SUMMARY

From 1908 through 1943, 189 children 14 years of age or less with exophthalmic goiter were seen at the Mayo Clinic. In most cases thyroidectomy was carried out at the clinic, but 14 patients were treated medically with results that were considered good in 10, fair, in 3, and poor in 1. Thyroidectomy was performed in 164 patients, 8 dying while in the hospital. Fifty-five patients were operated on during the period before medication with iodine was instituted, with 5 deaths. One hundred nine children have been operated on after having been prepared for operation with iodine, with 3 deaths, for a hospital mortality rate of 2.8 per cent. Since the use of iodine began, the late results after thyroidectomy have been satisfactory. In the group of 102 patients who survived operation done since the use of iodine was instituted, and on whom follow-up data are available, 1 patient died from the results of hyperthyroidism, 7 patients have had recurrent exophthalmic goiter, and 23 patients developed low basal metabolic rates or myxedema.

Fifty-two children 14 years of age or less with adenomatous goiter were seen at the clinic from 1917 through 1943. In no case was the

basal metabolic rate elevated and adenomatous goiter with hyperthyroidism has never been encountered in children at the clinic. Fourteen patients were operated on and the remainder were treated medically. The adenomas seemed to differ in no way from those found in the goiters of adults.

From 1908 through 1943, 53 children with nodular goiters were operated on here. In 32 cases the nodularity was caused by adenomas, in 3 cases by thyroiditis, and in 18 cases by malignancy. In 5 cases of carcinoma, enlarged cervical lymph nodes overshadowed the enlargement of the thyroid but, in the other 13 cases, the nodularity was largely confined to the thyroid gland. Thus, 1 in 3 nodular goiters in children, for which operation has been performed at the clinic, have been malignant.

In 17 of the 18 children with carcinoma of the thyroid gland, the tissue diagnosis was adenocarcinoma of malignancy either grade 1 or grade 2. Thirteen of the adenocarcinomas were of the papillary type, and 2 were noted to have developed in fetal adenomas. In 1 case the adenocarcinoma was of malignancy grade 4. The lesion was judged operable in 10 cases, inoperable in 8. In every case in which metastasis had developed, 11 in all, the cervical lymph nodes were involved; in 4 cases pulmonary metastasis developed and in 1 case metastatic tissue was found in the calvarium and spinal column. Whether the lesion was resected or not, irradiation therapy was carried out except in 1 case, in which death occurred following biopsy.

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GOITER IN THE SOUTHERN STATES

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GOITER is not common in the southern states. Although southern surgeons have contributed in a meager proportion to the literature on goiter, in recent years more and more papers have appeared from this section showing at last a growing realization that though most of the South is not an endemic goiter region, its peoples have goiter not infrequently and in some sections in surprisingly high incidence. In the coastal states of the South, goiters in Negroes offer unique problems not observed in like prominence in series from endemic goiter regions of the nation. The distribution of goiter in the South is irregular. In general the incidence is low, but in sporadic sections not truly goiter belts, more goiter is found than is average for the South. Goiter is probably encountered most commonly in the mountainous regions, particularly in the more thickly settled parts of the Appalachian range. Brenizer and McKnight[1] reported 7,500 goiter operations performed by them in Charlotte, N. C., over a period of twenty-eight years. S. L. Ledbetter,[2] of Birmingham, and Earle Drennen,[3] of Birmingham, each have performed over 1,000 operations for goiter. Scruggs[4] reported that in 123 hospitals affiliated with the Duke Foundation, or 85 per cent of the hospitals of North Carolina, there were 893 thyroid operations performed in 1938. Hayne[5] found goiters in 3.8 per cent of 17,600 people examined throughout South Carolina. Davison and Poer[6] reported 542 cases of goiter from the records of the Henry Grady Hospital and from their own practice in Atlanta covering a period of ten years. They stated that during 1935 there were only 350 operations for goiter in the entire state of Georgia. In 1939, Mahorner and Barrow[7] reported 248 patients with goiter among 52,863 patients admitted in one year to Charity Hospital in New Orleans (1 to 213). Only 105 patients of this group were operated upon for goiter. Lehman and Shearburn[8] found 401 surgical goiter patients among 87,661 admitted to the University of Virginia Hospital over a period of twelve years. Less than 0.1 per cent of men from the southern states examined for the draft in World War I showed goiter,[9] whereas, in the same draft examinations from 1.5 to 3 per cent of the men from the Northwest and Great Lakes Regions were found to have goiter. All of these reports from different sections of the South attest to the relative infrequency of goiter and to the few surgeons with large experience in this field. In spite of the fact that goiters are not as common as they are in endemic goiter regions, thyroid diseases of all variety and all degrees of severity are encountered in the South.

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Goiters occur more frequently in the southern part of Louisiana than in the central and northern areas of the state. Olesen[10] in his report on the distribution of endemic goiter in the United States revealed some astounding figures. In parishes (the counties of other states) in the southern part of Louisiana the incidence of goiter in children was stated to be from 35 to 55 per cent in boys and from 38 to 70 per cent in girls. This estimate is far from correct. Even though it is well appreciated that more goiter is found in the flat southeastern part of Louisiana, it is obvious to those of us who see patients from the parishes around New Orleans, that goiters are not as common as Olesen's figures indicate.

I computed[11] the number of goiter patients admitted in 1938 to three charity hospitals in Louisiana, at Lafayette, Shreveport, and New Orleans. They were divided according to the parish from which they came. The number of patients admitted from southern parishes was greater than the number admitted from other sections; and this not only was true of total number of patients admitted, it was also true expressed as the incidence of goiter per 10,000 inhabitants of each parish. Thus from Orleans parish there were 1.9 per 10,000, from Lafourche, Terrebonne and St. Bernard parishes adjacent to Orleans there were 2.15, 3.0, and 5.5, respectively, per 10,000 inhabitants. In northern parishes the incidence was 0.5 to 1.5 per 10,000. This is admittedly a very gross and inexact method of estimating the distribution of goiter, mainly because it is incomplete, does not include all hospitals, and does include only indigent patients of the state in one year. However, these findings corroborate the impression long since held by the profession of this community that goiter is not uncommon among peoples inhabiting the banks of certain bayous. These rivers, often very deep, were originally estuaries of the Mississippi River. The surrounding lands are flat and low and frequently marshy and were formed by alluvial deposits of the Mississippi River. The diet of the people inhabiting this area consists presumably of much sea foods, and the iodine content of their vegetables is relatively high. The people themselves along these bayous recognize that nodular goiters are common. The explanation as to why the people in this low flat area should have more goiters than those in the rest of Louisiana is not available. All the soil of this area was brought down the river possibly from the upper Mississippi and the Ohio Rivers, which drain goiter belts. A positive goiterogenic factor thus may have been transported, but another engaging thought is the possibility of a negative factor being responsible for the goiters. The water supply for many of these families is rain water from cisterns.

Many reports from the South show a high mortality for thyroid surgery. This in general is true and has usually been explained by less experience with the management of the disease. However, there is danger of being overapologetic for the higher mortality, for a few

southern surgeons record mortality rates for thyroidectomy which are unsurpassed in excellence. Drennen[12] in Birmingham reported 300 thyroidectomies with 1 death. In his entire series of over 1,100 operations for goiter, he has had but 5 deaths,[3] a mortality of less than one-half of 1 per cent. Ledbetter[2] in the same city, since 1929, has performed over 1,400 operations with no deaths. Scruggs[4] of Charlotte, N. C., reported 256 operations for goiter with 1 death. While these three series are not large, they attest to excellent surgical judgment and technique.

Fig. 1.—A Negro woman, aged 58 years, with severe exophthalmic goiter before, and one year after, operation. The operation was done in stages under unfavorable hospital facilities with good result. Goiters of this type in the Negro race deserve management with extra caution.

Many southern authors have called attention to the higher mortality in Negro patients. Goiters occur as frequently or more frequently in the Negro race than in the white race.[11] Lehman and Shearburn reported 401 thyroidectomies in a twelve-year period at the University of Virginia Hospital. The mortality was almost entirely in the Negro race. The mortality figures for white patients was 0.84 per cent and for Negroes 9.4 per cent. They could not explain the higher mortality in Negroes after an analysis of data, and they believe that the disease in the Negro may be surgically a separate problem. Bigger[13] also admitted a higher mortality in the Negro and thinks it due in part to malnutrition and vitamin deficiency in that race. Maes, Boyce and McFetrich (1936)[14] reported the total mortality for thyroid operations as 5.7 per cent in the Charity Hospital series. The deaths (medical) from goiter in patients not operated upon for the same period exceeded the postoperative deaths. In Negro men with toxic goiter the mortality for thyroidectomy was 25 per cent. Maes believes that thyroid disease is a severer and graver condition in the Negro man than the same disease in white individuals. In a later publication Boyce[15] reported 817 surgical thyroid cases from the same institution (Charity Hospital) and again called attention to the high mortality in the Negro. The total mortality was 5.3 per cent. The mortality following thy-

roidectomy for toxic goiter was higher in the Negro race (12.58 per cent) than in the white race (6.93 per cent). He says the reason for this disproportion existing baffles explanation. Herrmann[16] reported 40 Negroes among 729 patients with goiter admitted to the surgical service of the Lakeside Hospital, Cleveland. He could find no difference in the severity of the disease or in the response to treatment between Negro and native white people. While it is true that various series show a higher mortality for thyroid surgery in the Negro, a higher mortality for hyperthyroidism in the Negro without surgery has not been reported. Should this be true it would be a significant finding, particularly in such series as those from Charity Hospital where the medical deaths exceeded those following surgery.

Fig. 2.—A Negro woman, aged 38 years, before and after operation for a huge toxic nodular goiter (weight approximately 600 Gm.). The substernal portion was also very large. On admission she had cardiac decompensation. She came from lower Mississippi where goiter is not common. This is an example of the extent to which sporadic goiter may develop in a nonendemic area. She became perfectly well following thyroidectomy.

I have had a higher mortality for thyroidectomy in Negroes, however, my impressions of the causes for this are not in accord with some of the previously expressed reasons. As far as I can observe the disease is similar in course and average severity in the Negro. The response to preoperative preparation is less prompt and less decided in the Negro, but that in my experience is due to less favorable physical surroundings such as noise, crowding, too many visitors, and ward hospitalization in very hot, poorly ventilated space equipped only with basic essentials. Facilities entirely devoid of luxuries may be of no significance in the favorable outcome for most patients, but for the severely sick patient a luxury may become an essential and be a deciding factor in recovery.

During 1942, 1943, and 1944 (through October) on my services at Touro Infirmary, the Baptist Hospital, and the Eye, Ear, Nose, and Throat Hospital, I performed 110 operations for goiter on 101 patients. Seven of the patients had multiple stage operations (two patients had

three operations). This is a very small group of patients, but in this section of the country it may not be considered small and is representative of goiters as they are encountered here. Indeed, practically all variety of goiters were encountered.

Sixty-one patients represented the white race whereas forty were Negroes. There were only 7 men to 94 women, a ratio of 1 to 13.

Fifty-five of the patients had toxic goiters and forty-six nontoxic nodular goiters. The pathologist reported Hashimoto's disease in two instances. Four patients had substernal goiters. One patient with a toxic goiter was a child (girl) aged 13 years.

Of the patients who had multiple stage operations, five were white and two were Negroes. Two patients died following operation. Both were colored women with toxic diffuse (exophthalmic) goiters. Both deaths occurred postoperatively within two days, presumably of thyroid crises. These two deaths were both preventable and could have been avoided by stage operations. Other patients in this group were more severely toxic and were graver risks, yet they were carried successfully through their operations. Each of the two Negro patients who died had far less favorable physical surroundings for their illness, yet I must admit that the judgment as to the time and extent of operation was exerted just as if they were surrounded with the excessive luxuries afforded by many of the other patients in this group. The deficiencies in the facilities of the Negro patients should be countered with more cautiousness, which means more prolonged and more careful preparation and more frequent stage operations, not fewer than in white patients.

In my experience it has not been possible to produce conditions for Negro patients entirely favorable to surgery for toxic goiter. The economic part is largely the answer, for even though they may be very sick, a bed in a ward together with patients with various other conditions, entailing the commotion and excitement of visitors and many people in the room at one time, is frequently the best condition available for the important period of preoperative preparation and postoperative care. Even if the economy factor could be obviated there are others which often prevent optimum conditions and facilities being arranged for some of these very sick patients. Moreover, in the Negro there is an additional chance on the part of the surgeon for misjudgment of the proper time and extent of operation in toxic goiter. Ordinarily the Negro tolerates surgery well. His constitution and endurance are usually good. This should not confuse one but it probably has confused many. Moreover, no matter how sincerely the surgeon wishes to ignore them for better evidence upon which to base the soundest judgment, economic conditions in this day of crowded hospitals, even if the patient is provided for by eleemosynary funds, sometimes influence judgment to hasten the operation date. Other factors resulting from the relative infrequency of the condition in the South, such as technical errors, contribute to the higher mortalities, but it appears

that the main lesson to be learned from these repeated reports of higher mortality in the Negro is a lesson in judgment, namely, the necessity of being more wary, more cautious, when dealing with goiter in that race than when dealing with a condition of similar severity in a white patient. It is already well established that elderly individuals and children do not tolerate operation as well as those in middle decades. Goiter in the Negro should be added to these groups to emphasize the increased cautiousness which might be absolutely essential to obtaining a satisfactorily low mortality. This is not, as it might seem, a contradiction; the risk for the Negro race is still equivalent to the risk for the white race, but extra precautions must be taken to offset the physical handicaps in their hospitalization and other elements in judgment as to the proper time and the proper extent of operation.

SUMMARY

Goiter is not common in the southern states. It occurs most frequently in the mountainous areas. A few southern surgeons, however, report mortality rates for thyroid surgery which are unsurpassed in excellence.

The mortality for thyroid surgery in the Negro is in general higher than that for white patients. Poorer facilities for hospitalization and impetuous judgment may be the dominating factor in this higher mortality rate. A group of seventy patients from my private services is reported.

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THYROIDITIS

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THYROIDITIS, when defined as the reaction of the thyroid gland to injury, is commonplace. Degenerative changes with subsequent fibrosis are demonstrable in most nodular goiters and probably play an important part in the formation of the nodularity. The thyroid is a labile organ and responds functionally in the maintenance of oxygen consumption at a certain level. Frequently in physiologic and pathologic states of stress, such an increase in function is required in the maintenance of homeostasis. With this increase in function there is often a demonstrable morphologic alteration in individual cells and even groups of acini.[1] As a result of the interplay of several factors residual damage may be seen as evidenced by change in acinous size and shape, extravasation of colloid into the surrounding stroma, vascular damage, fibrosis, and even calcification. These changes are characteristically seen in nodular goiters and, in the broad sense, represent inflammation. In this consideration of the subject of inflammation of the thyroid gland, however, thyroiditis will be discussed in which the inflammatory process per se is apparently the cause of symptoms. These are usually encountered clinically under three main types: (1) acute suppurative thyroiditis; (2) acute nonsuppurative thyroiditis; (3) chronic degenerative thyroiditis.

ACUTE SUPPURATIVE THYROIDITIS

Acute suppurations are of bacterial origin, and strangely enough, are extremely uncommon, when compared to the frequency of metastatic abscesses in many other organs of the body. The thyroid gland seems to possess a definite resistance to local infection. In unpublished work, Cole and I[2] found that when pure cultures of streptococci and staphylococci were injected directly into the superior thyroid artery of dogs, abscess formation rarely followed. This was the experience of Roger and Garnier[3] in a more elaborate series of experiments. And yet these infections are obviously embolic when they do occur, either being associated with a generalized septicemia or following shortly after an acute infection in the pharynx or upper respiratory tract. The most common organisms encountered are the staphylococcus and streptococcus groups, although almost any type may be present. We have encountered the colon bacillus on two occasions and the typhoid bacillus once.

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The onset of the disease is often abrupt, being associated with chills occasionally, but always fever and local evidence of inflammation. Pain is the outstanding symptom. Because of the close relationship with the ribbon muscles of the neck, and the resulting spasm of these structures, the patient prefers to keep the neck in flexion, often in a sitting posture. Swallowing is painful and even hoarseness may be encountered. While the abscesses at first may be multiple, they are generally limited to one lobe or the isthmus. As a result, along with the diffuse swelling present in the neck, there may be present eccentric swelling. Where the isthmus of the thyroid is involved the depression above the sternal notch is often filled. The thyroid gland can usually be palpated but the outlines are masked by edema, and examination is difficult because of tenderness.

The systemic reaction to the infection is usually marked, perhaps due to the organ involved as well as its relation to the respiratory tract. Rupture into the trachea may occur but this is rare. If untreated, extension into the deep spaces of the neck is the most common sequela, and this is of grave consequence.

Since the advent of chemotherapy, acute suppuration of the thyroid gland is becoming less frequent. However, when an abscess does occur, surgical drainage is indicated along with suitable chemotherapeutic measures. Adequate oxygen intake is of the greatest importance and the use of the oxygen tent is advisable. The surgical incision must give adequate drainage, and this will entail a good exposure of the part. At the same time, care must be taken not to break through the inflammatory barriers of the neck more than is necessary, and in particular, pathways to the mediastinum must be protected.

Cases are on record in which so much thyroid tissue was destroyed by the infection that myxedema resulted. This, however, is extremely rare, and a good result should be obtained although this, to a large extent, will depend on the severity of the generalized infection, of which the suppuration in the thyroid is a part.

ACUTE NONSUPPURATIVE THYROIDITIS

Nonsuppurative acute thyroiditis is seen more frequently than the suppurative type, and yet very little is known about it. It is recognized by its clinical manifestations, but surgical interference is seldom indicated, and adequate bacteriologic and morphologic observations are, therefore, not available. In view of the fact that about one-half of the patients will give a history of recent upper respiratory tract infection and that occasionally the process goes on to suppuration, it is probable that the instigating factor in the inflammation is bacterial.

The symptomatology resembles the suppurative type in character, but not in extent. The onset is not so abrupt and the general manifestations are mild. Fever is slight or absent. The thyroid is enlarged and tender, but swelling and tenderness throughout the soft tissues

of the neck are not pronounced. There is discomfort on swallowing or movement of the neck, but often the patient is able to continue his ordinary duties.

Except for those rare cases that terminate in suppuration the lesion is, for the most part, self-limited and subsides in from ten days to two weeks. Chemotherapeutic methods will be of more value in this type of thyroiditis.

When thyroiditis occurs in a nodular organ the term strumitis has been applied. It is doubtful whether such a separate classification is of use, except in one instance—hemorrhage. Spontaneous hemorrhage is most unusual in a normal gland. It is not uncommon in a nodular gland, and at times the nodule may be so small as not to have been previously recognized by the patient. Hemorrhage into the stroma of the thyroid gland sets up an inflammatory response, chiefly monocytic in type. This inflammation is generally limited to the environs of the nodule involved, and presents itself chiefly as tenderness. There is often a history of straining or shouting, followed some hours later by the continuous enlargement of one lobe or a nodule in one lobe for several days. The lesion is much more common in young adults. It requires no immediate treatment. After resolution of the hemorrhage the thyroid should be treated as any other nodular gland.

CHRONIC DEGENERATIVE THYROIDITIS

Chronic degenerative lesions are heterogeneous. They include a considerable number of variants of fairly definite pathologic patterns, the nature of which is not too clear-cut. From the pathologic standpoint, four striking lesions are seen: namely, a remarkable lymphocytic overgrowth in the thyroid; fibroplasia; the presence of giant cells with a surrounding inflammatory zone, faintly suggestive of tubercle formation; and a distinctive type of acinous change in which the nuclei and cytoplasms enlarge and then slowly degenerate. Efforts have been made to correlate these pathologic changes with the clinical picture of the patient, but for the most part these syndromes are not too clear-cut.

One of the earliest reports of this type of thyroiditis is that of Semple in 1869.[4] Although his patient died of what was stated to be pulmonary tuberculosis, the microscopic appearance of the thyroid was described as "being made up principally of dense fibrous tissue. The fibers are those of ordinary connective tissue. They pass in all directions through the gland and in many parts completely obliterate its ordinary loculated structure. In other parts where the change is less advanced the loculi and their contained cells are still visible." There was also intimate attachment between the thyroid and the surrounding structures of the neck with obstructive symptoms.

A similar but more extensive lesion was described in 1885 by Bowlby.[5] This patient presented a gradually increasing enlargement of the thyroid gland with tracheal obstruction requiring tracheotomy three years

after onset. All of the adjacent structures in the neck and upper mediastinum were involved by a diffuse fibrosis and although microscopic examination revealed adult fibrous tissue, because of the manner of its growth the lesion was thought to be one of fibrosarcoma. There were no metastases, however, and the picture is not unlike that seen in advanced cases of fibrosing thyroiditis.

Neither of these reports received a great deal of attention, perhaps due to the fact that interest in the thyroid gland at that time was not very great. As surgery of the thyroid became more common, it was easier for Riedel, first in 1896[6] and later in 1897[7] and 1910,[8] to focus attention on the subject. Although one of the patients in his first report had a thyroid in which the presence of round cells was the predominant microscopic finding, and the "eisenharte" firmness of the gland on clinical examination often was not in keeping with its microscopic appearance, he was much more impressed by the fibrosis of the gland and its tendency to involve contiguous structures as it developed. He was also impressed by the inflammatory nature of the condition and its usual benignant course.

Inflammation in which the thyroid tissue was to a large extent replaced by lymphoid tissue was described in 1912 by Hashimoto.[9] In reporting four cases, he called attention to the frequency of this finding in older women, the involvement of the entire gland, the lack of involvement of contiguous structure, the absence of obstructive symptoms, the tendency toward postoperative hoarseness, and a long convalescence. Microscopically, the lymphoid tissue was so abundant that he chose the name "struma lymphomatosa" for the lesion, and considered it different from that described by Riedel both clinically and pathologically.

In 1922, Ewing[10] referred to his experience with four cases of thyroiditis and was of the opinion that the pathologic changes described by both Riedel and Hashimoto could be found simultaneously. He suggested that the fibrosis so apparent in the Riedel type of lesion could be the end result of the picture described by Hashimoto.

This was the opinion also of Williamson and Pearse,[11] who termed the lesion "lymphoadenoid goiter" and looked upon the accumulation of lymphoid tissue as related to what they termed the "lymphogenic" function of the thyroid. The fibrosis they considered a creeping replacement of injured reticuloendothelium.

In 1931, Graham and McCullagh[12] reported upon observations of their own concerning struma lymphomatosa and reviewed the cases presented by Hashimoto. This represented perhaps the most critical study of the subject to that date, and their insistence that the two types of thyroiditis described by Riedel and Hashimoto were separate clinical and pathological entities was well supported. This has been the opinion of many who have published reports on the subject since, and while there are those who would disagree,[11, 13, 14] the two lesions

are generally considered at the present time as representing different pathologic pictures, and presenting different clinical syndromes.[12, 15-23] A critical opinion, however, on the evidence in support of two distinct pathologic entities is certainly equivocal.

When these lesions are considered as separate entities, the dominant characteristic of Riedel's disease is fibrosis. In about one-third of the reported cases, this has been limited to one lobe or a part of one lobe. Extraglandular fibrosis, however, is present in later stages as has been seen in earlier reported cases. The involved gland is hard and white and usually not appreciably enlarged, although when the surrounding muscles and large vessels are involved, the outlines of the gland are not too distinct.

In the earlier stages, this fibrous tissue may be very cellular and there is a considerable infiltration of cells of the lymphocytic series often with follicle formation. Supposedly, one of the most characteristic features is the thyroid parenchyma. It is often enmeshed in the fibrosing process, but the thyroid acini are said to be normal. This has not been our experience. Careful study of the thyroid acini has shown definite evidence of cellular injury in most instances and this injury has resulted in hyperplasia, metaplasia, and what apparently is the retention of secretory products in the cytoplasm resembling the so-called Hürthle cell. Cell death is the end result. This may be gradual, the acinus becoming smaller and smaller, or many cells may degenerate at once leaving unabsorbed colloid in the stroma. At such time, giant cell reaction is present, and the giant cell often takes on bizarre appearances because of the resemblance of the colloid to its cytoplasms. It is quite possible that the rapidity of this process may determine the degree of the inflammatory reaction.

The most conspicuous clinical features are related to the fibrosis. If this is mild, a slightly enlarged, very hard gland may be the presenting symptom. As fibrosis progresses, and more thyroid tissue is destroyed, evidence of hypofunction of the gland may be present. Often in the very early stages, however, a slight hyperfunction may exist for a short while. Invasion of adjacent structures by the fibroblasts brings on symptoms of obstruction. Compression of the jugular veins with resulting edema, and pressure on the esophagus causing dysphagia are usually earlier than severe tracheal obstruction. When the lesion is limited to one lobe, respiratory difficulty may appear, due to tracheal displacement. Recurrent laryngeal nerve involvement is extremely rare.

The most difficult lesion to exclude is cancer, and while often one may make the presumptive diagnosis of Riedel's struma, certainty is usually not established until operation, and even then microscopic examination of the tissue may be necessary. The massive fibrosing type is extremely rare, apparently may occur in the relatively young although this has not been our experience, and males are frequently affected.

The treatment is entirely related to relief or prevention of obstruction. When only one lobe or a part of a lobe is involved, resection of

this lobe and the isthmus is generally feasible. Where the entire gland and contiguous structures are involved, subtotal resection is usually fraught with considerable danger and removal of the isthmus in order to free the trachea may be all that can safely be accomplished. There have been several favorable reports from the use of x-ray therapy but this has been with the more cellular type of lesion.

The classical picture of struma lymphomatosa as it is generally considered presents several differences. The entire gland is usually involved when the patient first presents herself, although not necessarily so. The gland is lobulated, very thick, and the surface smooth. The only extraglandular attachments encountered are tracheal, and these never extensive. This gross picture is easily explained when the gland is studied microscopically. The yellow trabeculated, meaty appearance of the cut surface is due to lymphoid overgrowth. Lymphoid follicles are prominent, but the lymphocytes themselves as well as the structure of the follicle differ in type in no way from those encountered less extensively in exophthalmic goiter, status thymolymphaticus, or even Riedel's struma. The chief difference appears to be a quantitative one. In the earlier stages the gland is friable, but later it is more resilient as fibrosis increases. One of the impressive microscopic lesions is in the thyroid parenchyma. The Hürthle cell type of degeneration described in Riedel's struma is much more marked and almost universal. Giant cell reaction about the colloid is also more pronounced. Fibrosis is present in varying amounts and it is perhaps the relationship between the relative amounts of lymphoid follicle tissue and fibrosis that has led to most of the confusion in classifying various types of thyroiditis.

The clinical picture associated with the type of lesion found in struma lymphomatosa has been for the most part vague and associated with the mild compressive symptoms that one would anticipate. Neither hyperthyroidism nor hypothyroidism are, as a rule, outstanding in most early cases. After thyroidectomy, hypothyroidism is frequently observed. It is stated that these patients are practically always 50 years old or more. It is also generally stated that the lesion does not occur in men. One may readily question the statistical accuracy of such statements as being based on entirely too small a number of clinical observations.

Surgical extirpation of most of the gland has been the treatment of choice. Most operations have been performed with a mistaken diagnosis, and one may well doubt the value of surgical extirpation where obstruction is not important. Often hypothyroidism is the end result and this certainly is not prevented by surgery. Following thyroidectomy hoarseness may be present for many months. Where a diagnosis could be established, radiation has been reported to be of value.[24] It would seem that here, as in Riedel's struma, the chief damage produced by this lesion is that of obstruction, and here the indication for surgical extirpation must lie.

As has been stated there exists a considerable controversy as to the relationship between Riedel's struma and Hashimoto's type of struma lymphomatosa. In isolated, well-defined types, there seems to be a definite difference in the clinical picture. Clinical syndromes, however, owe their existence to underlying pathologic disturbance, and the answer to the question will be much easier to obtain by an analysis of the pathologic picture, rather than a study of statistical reports. It seems apparent from a consideration of the microscopic appearance of these two lesions that they present a quantitative, rather than a qualitative, difference, and the symptoms that ensue are related to the predominance of a particular type of inflammatory reaction. In Riedel's goiter, it is fibrosis; in Hashimoto's type it is lymphoid overgrowth. Often both have been noted in almost equal amounts, and this has led to discussions as to classification that have not been too illuminating.

It has been assumed by some that the fibrosis is an end stage of the lymphadenoid type, but evidence to support this very logical assumption is not too apparent. Observations have been recorded on cases in which microscopic studies have been made at intervals of two years[16] and thirteen years[25] with no great amount of change in the microscopic picture. It is therefore much more likely that they represent parallel manifestations of the same underlying injury.

Infections of various types have been thought at times to play a part in the production of these changes. Cultures of the glands whenever done have, for the most part, been sterile, and such changes were not encountered when bacteria were injected directly in the superior thyroid arteries of dogs and rabbits by Cole and me.[2] This does not mean, however, that infection may not play an indirect role. Upper respiratory tract infections have been frequently noted in the cases reported, and while this association may be fortuitous, it still must be borne in mind. It has been suggested recently[26] that Riedel's thyroiditis may be the result of a perithyroiditis with vascular occlusion. That it may be the result of iodine effect[14] has been considered, and McCarrison[27] has reproduced a lesion in rats showing a definite microscopic resemblance to struma lymphomatosa, by certain dietary deficiencies. McKnight[28] has suggested that the inflammation is secondary to an obscure biochemical irritant probably produced by the patient. None of these etiological concepts, however, fits the complete clinical picture.

As has been stated, the interstitial lymphoid nodules with their germinal centers differ in no way except in amount from those seen in other thyroid lesions and in particularly exophthalmic goiter. All of these lesions seem to represent functional aberration on the part of the entire gland or some of its cells, and wherever lymphoid hyperplasia is seen in the thyroid there usually is evidence of an unusual absorption of secretory products or of cellular degeneration and breakdown. It is not a constant finding with all functional atrophy, however, as it is not commonly seen following anterior lobe hypophysectomy in the experimental

animal or in Simmonds' disease. Again, as may be noted in Fig. 1, neither lymphoid hyperplasia nor fibrosis is seen in atrophy where the human gland has been exposed to large amounts of radiation. The loose acellular collagen here surrounds minute acini, and probably represents the result of the action of the irradiation on the vascular apparatus.

However, there are times in which an inflammatory reaction to colloid is most marked, and whether the colloid undergoes a chemical change as has been suggested by Mallory,[29] the reaction seems to be related definitely to its fatty acid content as has been demonstrated by Ferguson.[30] He showed that in disintegrating follicles as a result of the hydrolysis of the lipids in the colloid and epithelium an extensive inflammatory reaction may occur with giant cell formation, lymphoid hyperplasia, and fibroplasia. Goetsch, however,[31] believes the giant cells are

Fig. 1.—Effect of extensive x-ray therapy on thyroid showing changes secondary to avascularity. Note loose collagen fibrils and absence of dense fibrosis as well as lymphoid reaction.

composed of a syncytium of degenerating thyroid cells and are not phagocytic, and he interprets them as evidence of the degenerative process that takes place in Riedel's disease associated with the inflammatory reaction. Fig. 2 illustrates this type of parenchymatous change as seen associated with marked reaction to the colloid and the degenerating thyroid parenchyma.

Thus, degeneration of the thyroid cells and the colloid can be demonstrated as a fairly constant finding in chronic thyroiditis. The cause of this degeneration is not so easily found. Since this finding is so universally associated with function, endocrine interrelationships must necessarily be studied. Apparently the anterior lobe of the hypophy-

sis, the islets of Langerhans, the parathyroids, and the adrenal medulla play no part. The sex hormones have been inadequately studied to warrant any definite conclusions. The effect of the adrenal cortex is much more suggestive. Lymphoid hyperplasia in adrenal cortical insufficiency is an old observation, being most dramatically seen in the thymic enlargement that occurs in status thymolymphaticus. Pituitary adrenotrophic effect on lymphoid tissue mass has been recently demonstrated[38] as has the action of adrenal cortical hormone in experimental leucemia suggested hormone effect on the lymphoid systems.[39] Similar changes in the thyroid as we have noted in both the Riedel and the Hashimoto types of gland have been noted by many observers as being associated with adrenal cortical hypoplasia.[32-36] The adrenal lesion is more commonly that of a cytotoxic type of atrophy rather than that

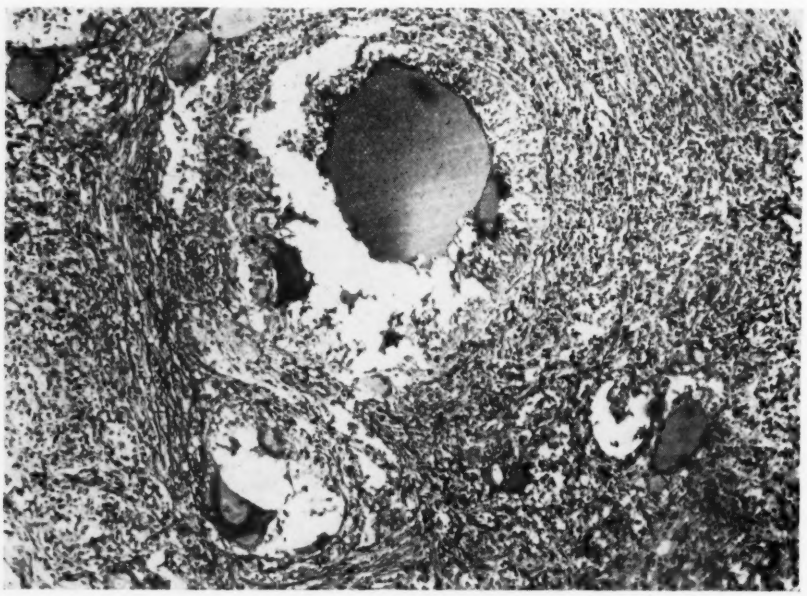

Fig. 2.—Inflammatory reaction to colloid. There apparently has been rapid epithelial degeneration. There are foam cells as well as giant cells around the colloid suggesting a reaction to lipids.

seen in tuberculous destruction. Figs. 3 and 4 illustrate the resemblance between the thyroid seen in such adrenal insufficiency and Riedel's struma, while Figs. 5 and 6 compare the Hashimoto type of thyroiditis with another area from the thyroid of the same patient with cortical insufficiency. When studied in great detail but little difference is noted. However, while it is not unusual to find such changes in the thyroid in this type of adrenal cortical insufficiency, these changes have also been noted in the thyroid in which the adrenal cortex was apparently normal. Jaffé has reported four such instances.[37] In each of his cases extensive lymphocytic infiltration was noted, and in two of them extensive fibrosis was present. In three of these cases the thyroid lesions

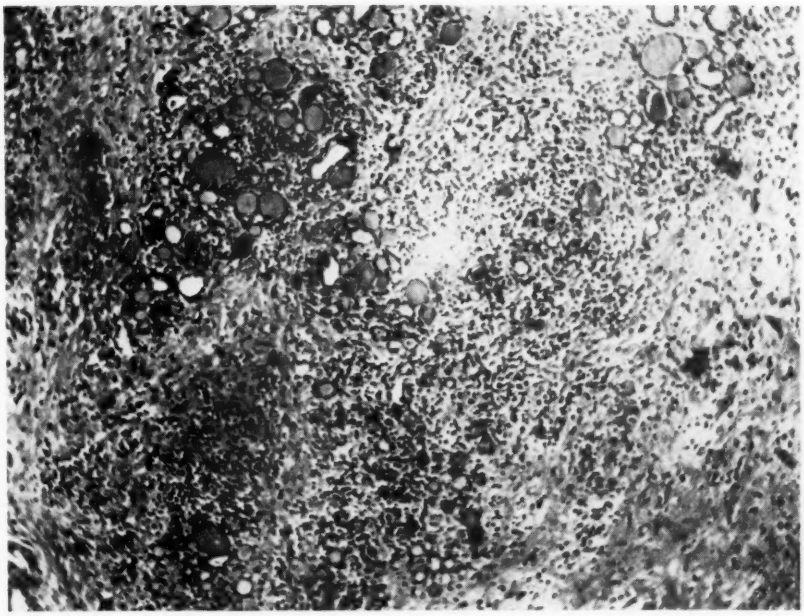

Fig. 3.—Area from Riedel's struma illustrating fibrosis and round-cell infiltration.

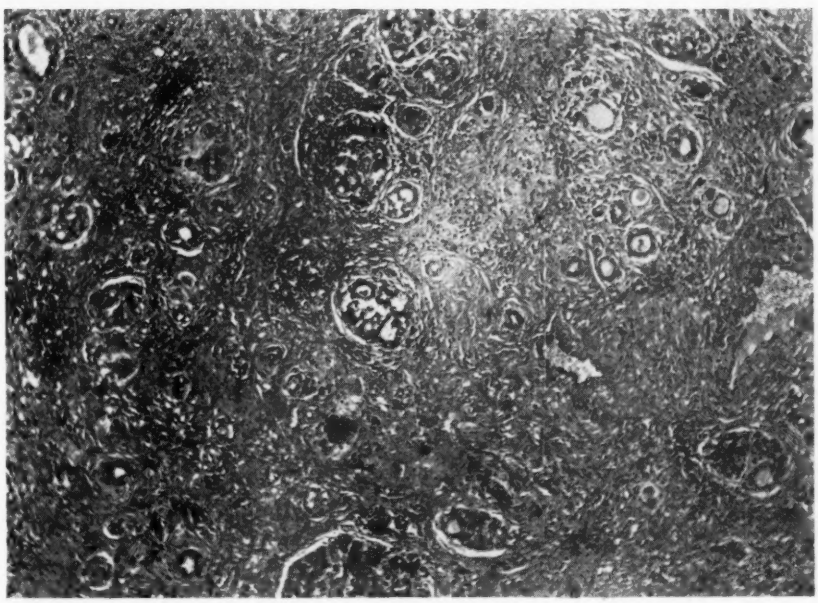

Fig. 4.—Area from thyroid gland of patient dying from cytotoxic type of adrenal cortical insufficiency showing similar changes to those encountered in Riedel's struma.

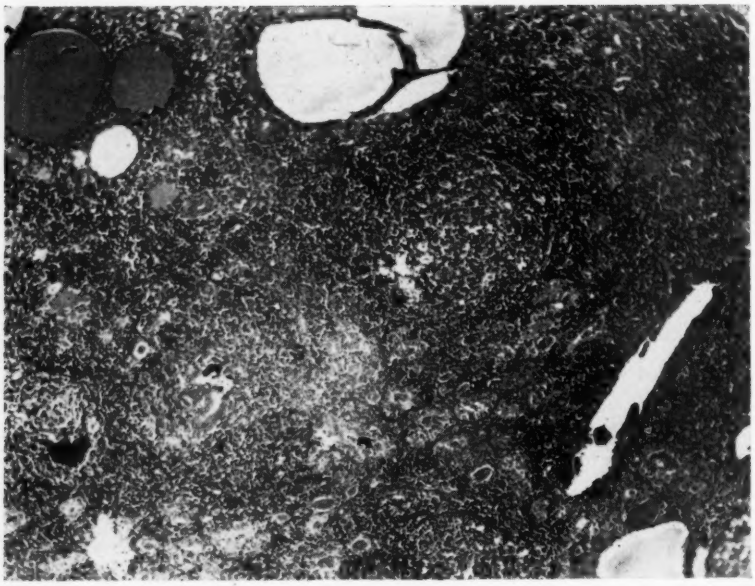

Fig. 5.—Massive lymphoid overgrowth as seen in Hashimoto type of thyroid.

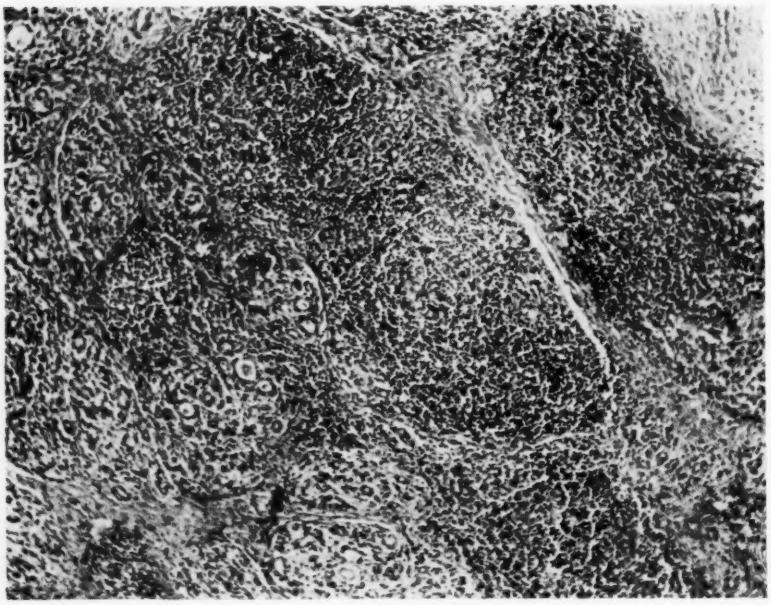

Fig. 6.—Lymphoid overgrowth and parenchymatous atrophy in thyroid of same patient as shown in Fig. 4. Compare with Hashimoto type of lesion seen in Fig. 5.

were incidental autopsy findings, with no symptoms referable to the thyroid, while the fourth showed evidence of myxedema. The changes noted in the adrenal were, for the most part, slight and consisted chiefly in alteration in lipid dispersion. He thus felt that the lymphocytic infiltration and fibrosis so often seen in the thyroid in atrophy of the adrenal cortex "is not secondary to the destruction of the cortex but is a separate, although coordinate, process." Furthermore, Scarcello and Goodale[25] have described the autopsy findings in a patient with struma lymphomatosa in which no gross lesion was noted in the adrenal glands. Detailed microscopic observations were not given in their protocol. The failure to note extensive morphologic changes in the adrenal, however, does not exclude functional alterations.

In summary, therefore, some aspects of Riedel's thyroiditis and Hashimoto's struma lymphomatosa must still remain controversial. Several features, however, are becoming definite. They both represent inflammatory processes, and are nonbacterial in origin. While clinically they may present divergent pictures as a result of the type of inflammatory change noted in the thyroid gland, pathologically this change is of the same basic type, and the diversions are quantitative rather than qualitative. The lymphoid overgrowth and the fibrosis are associated with a reaction to a peculiar type of parenchymatous degeneration which may be responsible for the inflammation, but may not be responsible entirely for the massive lymphocytic reaction. The cause of the degeneration of the thyroid cells needs to be investigated more fully. It is of great interest to note that identical changes in the thyroid are often seen in adrenal cortical insufficiency, even though at times they may also be present without demonstrable morphologic lesions in the adrenal cortex. Further studies of the endocrine relationships must be made, and in particular is there a dearth of information regarding the action of the sterid hormones of the sex glands.

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MALIGNANT GOITER

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MALIGNANCY is relatively rare in the field of thyroid surgery. However, it is important to know which types of goiter are likely to become malignant and which signs should arouse suspicion of malignant change. Cancer is almost unknown in exophthalmic goiter; indeed, so few cases have been reported that the diagnosis of exophthalmic goiter virtually eliminates the likelihood of its presence. In our series of 5,439 thyroidectomies there were 168 cases of cancer. Only one of these occurred in the exophthalmic type. It has been pointed out[1, 16] that although diffuse toxic goiter rarely gives rise to carcinoma, the microscopic picture in certain regenerative hyperplastic goiters is difficult to distinguish from that of malignant thyroid growths.

RELATION OF NODULAR GOITER TO CARCINOMA

With diffuse toxic goiter eliminated from consideration, it will be seen that the problem of cancer of the thyroid gland revolves about nodular goiter. The logic of this is apparent on contemplating the following facts. It has long been recognized and taught that a large proportion of malignant goiters have their origin in malignant degeneration of primarily benign and often long-standing tumors of the thyroid gland. Moreover, cancers of the thyroid, like those elsewhere, arise from a single focus, and in their local growth are seen as tumors or nodules rather than as diffuse infiltrations of the gland. Primary carcinoma arising in a previously normal thyroid gland, however, is probably not so rare as statistics would lead us to believe. Computed figures on this point are far from accurate for two reasons. First, many patients are unaware of the presence of fairly large goiters, and become conscious of them only when malignant change increases the rate of growth. Second, many primarily malignant goiters grow slowly or remain dormant for long periods of time. However, the mere fact that a tumor has existed for many years previous to its surgical removal does not necessarily indicate that the growth was benign at its inception. A recent review of the records of patients treated for goiter at the University of California Hospital during the past five years showed sixty-eight in which the history of pre-existing goiter seemed trustworthy. Of these sixty-eight, there were thirty-two in whom the history suggested very strongly that the tumor had been malignant from the onset. A number of patients were unaware that goiter had pre-existed the neoplasm, and in some the growth itself

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was discovered only after the removal of metastatic nodules in distant regions had led to examination of the thyroid gland. This illustrates that data obtained from questioning patients are notably inaccurate and may lead to false premises. In this connection, I reported thirty-six malignant goiters in 1930,[13] concluding that 94 per cent arose from goiters which had existed for varying periods of time before our examination, and that only two of the thirty-six were definitely not adenomatous in origin. In the light of recent experience, I now believe this conclusion to be unjustified.

The role played by pre-existing goiter as a source of carcinoma may have been decidedly overemphasized. However, in making a diagnosis of malignancy or suspected malignancy, too much stress cannot be laid on the significance of the nodular type of goiter. Almost all malignant goiters are nodular.

AGE

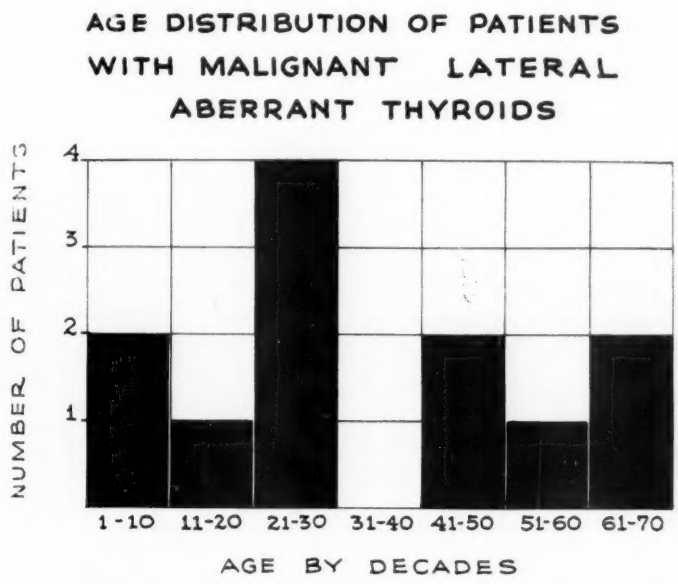
In general, the age groups of patients affected by carcinoma of the thyroid are comparable to those of patients affected by carcinoma of other organs. Approximately two-thirds of these patients are seen in the three decades between 40 and 70 years of age, while less than one-fifth are afflicted before the age of 40 years. There is, however, one rather remarkable feature which should be constantly borne in mind, namely, that malignancy appears in aberrant thyroid tissue at a much earlier age. The accompanying graphs show that in a previously reported series[16] the majority of malignancies occurring in laterally placed thyroid tissue were seen in patients under the age of 30 years (Fig. 1).

INCIDENCE

The frequency with which malignancy of the thyroid gland occurs has never been determined, and accuracy in such an estimate is impossible. There is little question, however, that geographical location and the incidence of nodular goiter are important factors in its production.[14] Wegelin[17] concluded that where goiter is endemic, malignant tumors of the thyroid occur in greater number. Wilson[18] pointed out that while autopsies in Bern, Switzerland, showed 1 death in 93 from malignant goiter, the figures from the United States revealed only 1 death in 928 from this type. The incidence of malignancy in surgically treated goiters varies from the high figures of 6.5 to almost 10 per cent reported by Kocher[9] and de Quervain[12] in Switzerland, to less than 1 per cent reported by Eberts and associates[5] in Canada. In the United States, the frequency is between 1.5 and 2.5 per cent. In my latest compilation of statistics, the incidence was 168 malignancies in 5,439 surgically treated goiters, or 3 per cent. Of these 5,439 cases in which pathologic specimens were available for examination, 1,900 could be eliminated as being of the diffuse type, leaving 168 malignancies in 3,539 cases, an incidence of 4.8 per cent.

SEX

An interesting feature of sex incidence which has not received sufficient emphasis in the literature is that, while the actual number of men with malignant goiter reported in all series of cases is less than that of women, the expectancy of carcinoma in men with nodular goiter is much greater. As I pointed out in 1935 and again in 1940, although the proportion of surgical goiters in men compared to women



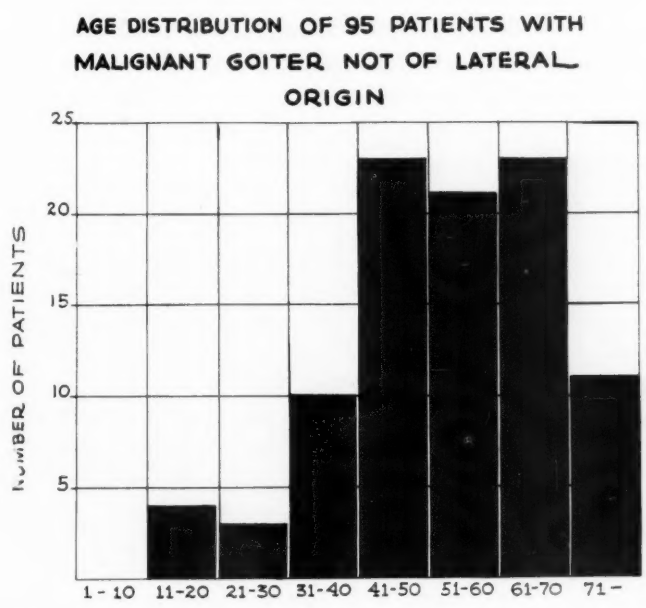


Fig. 1.—Graphs illustrating early age at which cancer of aberrant thyroid tissue is seen as contrasted with that of midline origin.

TABLE I

GOITER STATISTICS FROM UNIVERSITY OF CALIFORNIA HOSPITAL THROUGH 1943

SEX	SURGICAL GOITERS	TOXIC DIFFUSE GOITERS	NODULAR GOITERS	MALIGNANT GOITERS	MALIGNANT TO NODULAR GOITERS	
					RATIO	PER CENT
Male and Female	5439	1900	3539	168	1:21	4.8
Male	698	335	363	41	1:90	11.0
Female	4741	1565	3176	127	1:25	4.0
Male:Female	1:6.8	1:4.6	1:8.7	1:3		

is about 1 to 7, the ratio of malignant goiters is 1 in men to 3 or 4 in women. Thus, in this series of patients with nodular goiter, there was 1 carcinoma to each 17 men, but only 1 to each 44 women.

In the three years, 1941 to 1943 inclusive, there were 102 surgical goiters in men at the University of California Hospital. Seven of these proved to be malignant, an incidence of 1 carcinoma to each 15 patients operated upon. If the diffuse toxic goiters, of which there were 52, are eliminated, the almost unbelievable figure is obtained in men of 1 malignant out of each 7 nodular goiters coming to surgery, or 14 per cent. Table I shows the comparative rate of malignancy in men and women in the present series. The point to be kept in mind is that in men nodular goiter is many times more likely to be malignant than it is in women.

DIAGNOSIS

A definite preoperative diagnosis of malignant goiter should seldom be made. If one waits for the textbook picture, the time for surgical cure has passed. All diagnostic signs of malignancy are based upon penetration of the capsule of the gland and involvement of surrounding tissues. The hoarseness results from infiltration of the recurrent nerves; the fixation is caused by infiltration of the trachea or ribbon muscles; and the hardness is dependent upon the outward growth of cancerous tissue to replace normal, soft thyroid gland. Of these three cardinal signs, all can be found in benign nodular goiter. Although rare, paralysis of one or the other laryngeal nerve can be caused by pressure from a benign tumor. Davis[4] found this to be true in 0.4 per cent of cases. Fixation comparable to that accompanying infiltration of surrounding tissues can result from retrosternal and retrotracheal

TABLE II

PATHOLOGIC CLASSIFICATION OF MALIGNANT TUMORS OF THYROID GLAND SHOWING APPROXIMATE PERCENTAGE OF TUMORS IN EACH GROUP

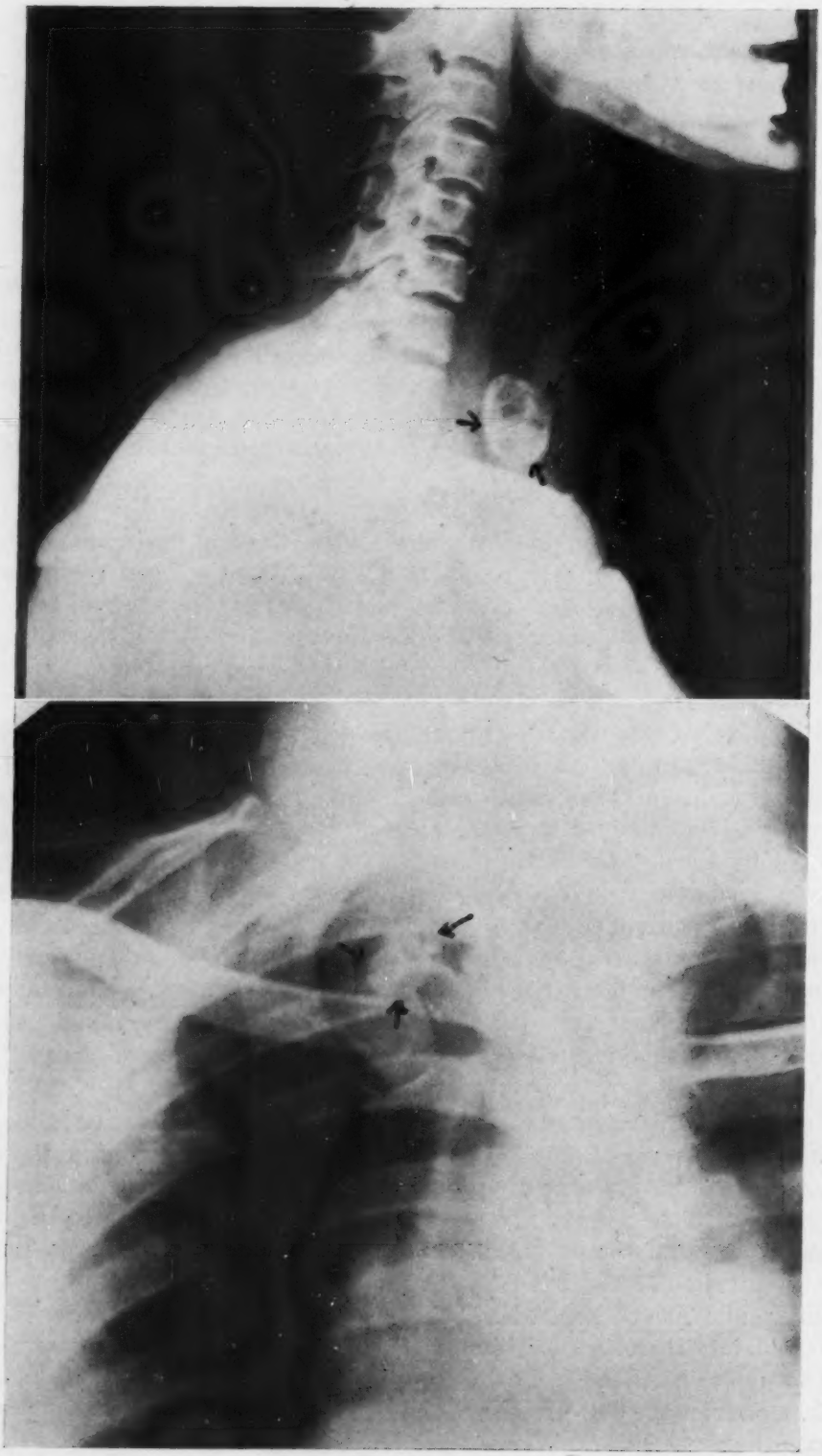
	PATHOLOGIC CLASSIFICATION	PER CENT
Group I (low malignancy)	Papillary carcinoma	36
Group II (moderate malignancy)	A. Malignant adenoma, Langhans	22
	B. Malignant adenoma, fetal	12
Group III (hopeless)	All others, including medullary, scirrhous, anaplastic carcinoma, sarcoma, and mixed types	28

extensions of benign adenomatous nodules. The same hard consistency as that encountered in malignant goiter will often be found in long-standing adenomatous nodules which have undergone calcareous degeneration. In this connection, however, it is not safe to assume that malignancy is absent because calcification in portions of the thyroid gland has been demonstrated roentgenologically. Carcinomatous and calcareous degeneration in the same nodule (Fig. 2) is not infrequent. Carcinoma may be suspected from the history alone in cases in which a long-standing or slowly growing tumor begins to increase rapidly in size and produce pressure symptoms. Operative treatment should be recommended on presumptive evidence of this kind, and should not be deferred until the previously mentioned cardinal symptoms have developed. As will be pointed out in the discussion of prognosis, no delay is justified in order to assure a more certain diagnosis.

PATHOLOGIC TYPES

There have been almost as many classifications of malignant neoplasms as there have been students of the subject. From a clinical point of view, the simplest classification which aids the surgeon to arrive at an accurate prognosis and institution of adequate therapy is the best. Most of the confusion in classifying cancer of the thyroid gland arises from a lack of uniformly accepted criteria of malignancy. Without going into detail regarding the different arrangements in use, suffice it to state that these tumors must be grouped according to their characteristics of growth as well as their microscopic architecture. Any classification is difficult because of the extreme variability presented by the lesions and the absence of a definite dividing line between benignancy and malignancy as judged by histologic studies. Criteria of malignancy based on cytologic changes alone are notoriously unreliable. The invasive qualities of a tumor have come to be recognized as the most dependable indication of the presence of malignancy, as well as of its degree. Without this invasive quality, an encapsulated tumor cannot be said to be malignant, regardless of its microscopic pattern.

A universally accepted classification would be of the greatest advantage in comparing parallel series of cases reported by different authors. Most writers have accepted Graham's[6] criterion of malignancy, namely, invasion of blood vessels. To this has been added as definite evidence of malignancy, invasion of the capsule of the adenoma, of its lymphatics, or of surrounding thyroid tissue and muscle. The classification used by Clute and Warren[2] is valuable. In their arrangement, cases are roughly divided into three grades: those of low or potential malignancy, those of moderate but not hopeless malignancy, and those of extreme or hopeless malignancy. The grouping used by me[15] is still simpler; it is based upon the reports of many observers that papillary tumors of the thyroid show the best prognosis. For this reason, all papillary tumors are



A.

B.

Fig. 2.—Roentgenograms *A* and *B* illustrating calcified areas in carcinoma of thyroid gland.

placed in a separate classification, irrespective of their origin in adenomas, aberrant thyroid tissue, or the gland proper. Since few carcinomas of the thyroid show a pure cellular pattern, and since the response to radiation therapy as well as the prognosis is peculiarly dependent upon the presence and amount of papilliferous tissue, this classification is based upon the presence and proportionate quantity of such tissue in the tumor. Roughly, from a prognostic and therapeutic standpoint, it is practical to arrange thyroid tumors in the following groups: Group I, papillary carcinomas; Group II, malignant adenomas; Group III, all others, including scirrhous, small cell, and large cell types, undifferentiated carcinomas, and those which display a sarcomatous tendency (Table II).

Group II is based upon gross findings, namely, an adenoma which has undergone malignant degeneration. In order to compare this series with those of Continental observers, our group has been subdivided arbitrarily into: A, Langhans' struma, those tumors showing the picture described by Langhans as proliferating adenoma (wuchernde Struma); and B, all other malignancies arising in an adenoma called "fetal" for lack of a more descriptive term. Fig. 3 illustrates variations of the papillary design, Fig. 4 typical Langhans pattern, and Fig. 5 a number of the more anaplastic tumors included in Group III. In the following section it will be seen how this classification is of value in reaching a more accurate prognosis.

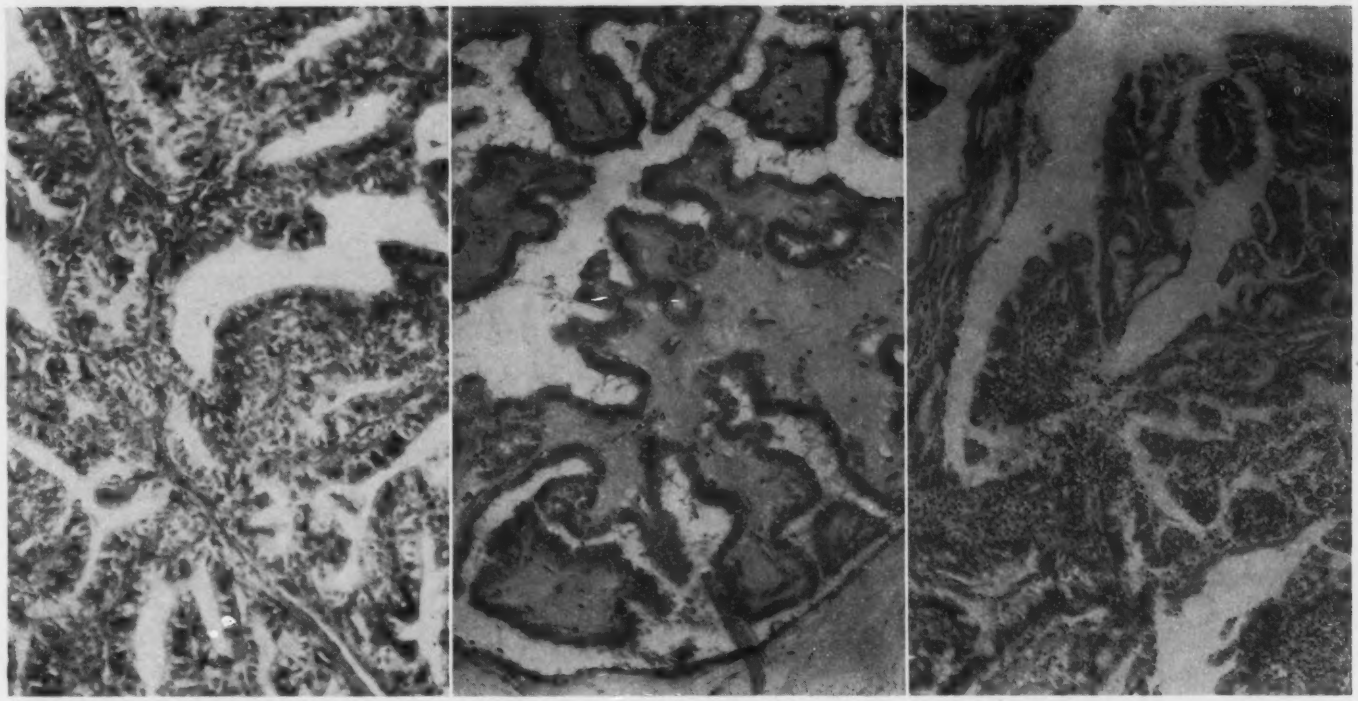
PROGNOSIS

There are three principal factors upon which prognosis is based. These are the time of diagnosis, the pathologic pattern, and the presence of metastasis. A recent survey of the material available to me has shown, as would be expected, that the easier the diagnosis the worse the prognosis. By dividing patients into three groups, as shown in Table III, it will be seen that of those bearing a preoperative diagnosis of malignancy or suspected malignancy, only 20 per cent survive for five years or longer. Of those in whom the malignancy is discovered first at the time of operation, 40 per cent survive five years. Eighty per cent in whom malignancy is first demonstrated upon section of the specimen removed live for five years, only one in five being likely to suffer recurrence. This is understandable when it is recalled that diagnosis before operation is based on involvement of extrathyroid tissue, diagnosis at

TABLE III

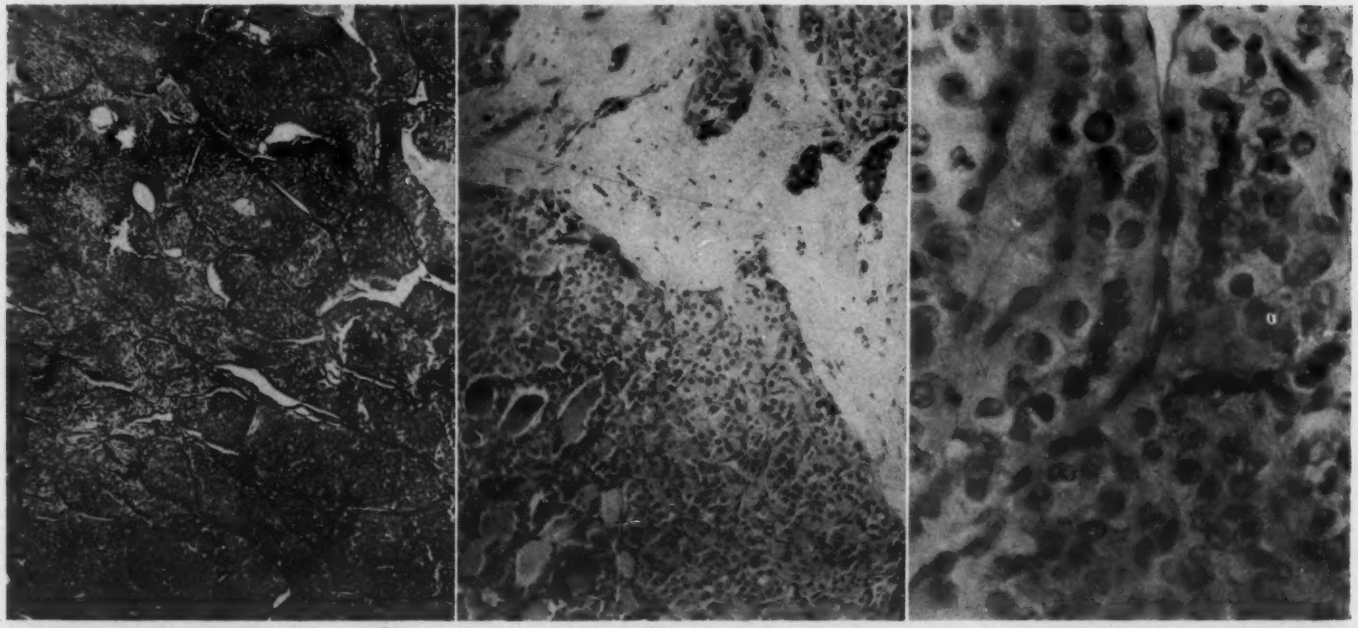
PROGNOSIS

	AFTER 5 YEARS	
	PER CENT DEAD	PER CENT LIVING
Group I (carcinoma diagnosed or suspected)	80	20
Group II (carcinoma diagnosed at operation)	60	40
Group III (diagnosed first on pathologic examination)	20	80



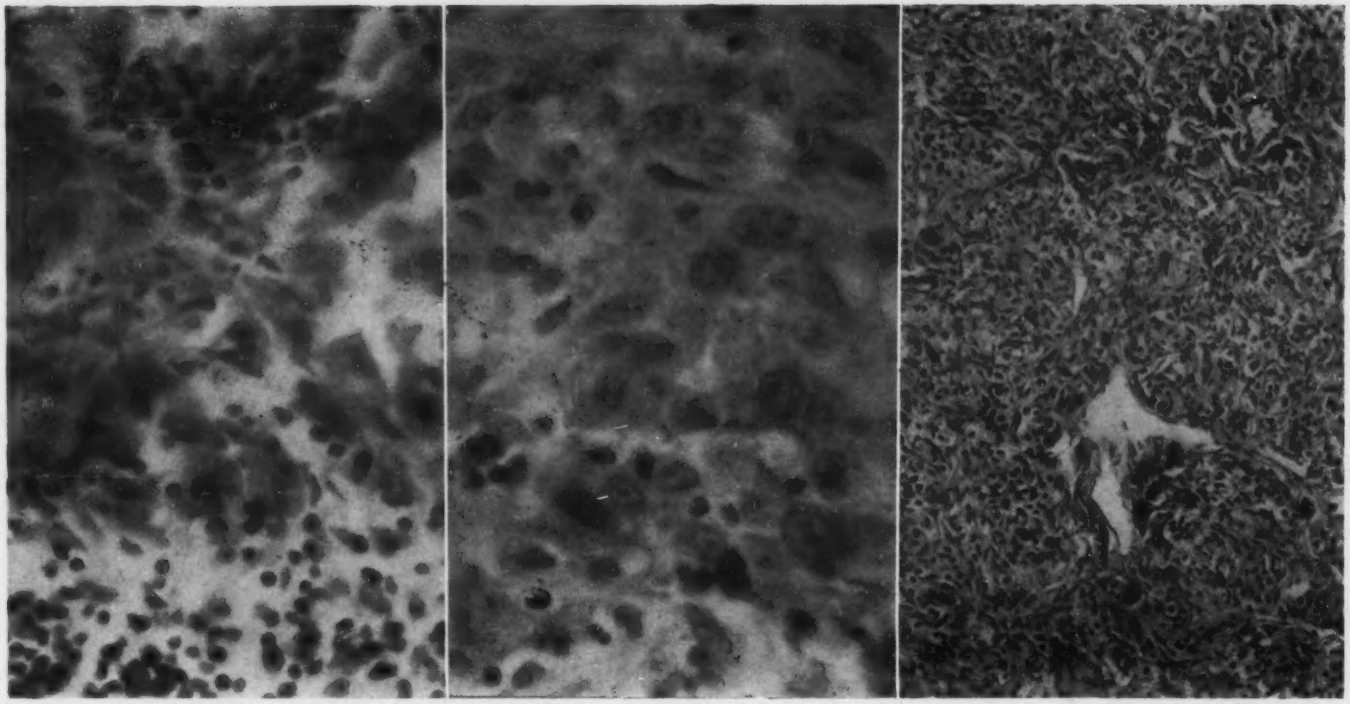
A. *B.* *C.*

Fig. 3.—Three examples of papillary tumors. *A* (×120) is from patient (Case 74) in whom papillary tissue was mixed with anaplastic tumor which caused death in three months. *B* (×120) is from patient (Case 20) who survived eleven years, responded well to irradiation, and died of pleural infiltration from anaplastic metaplasia of original tumor. *C* (×80) is from patient (Case 9) who should have responded well to modern radiation therapy, but was operated on twice for recurrences and died eight months after original operation.



A. *B.* *C.*

Fig. 4.—Three representative views of malignant adenoma, Langhans. *A* (×80) is from a Swiss patient and is typical of original Langhans' description. *B* (×80) is from the 9-year-old boy whose chest films are shown in Fig. 7. *C* (×450) is from lateral deposits in neck of 16-year-old girl, who has now reached 30 years of age without signs of recurrence.



A. *B.* *C.*

Fig. 5.—Three tumors of Group III, hopeless malignancy. *A* (×450) is a small-cell carcinoma from a patient (Case 16) in whom thyroid alveoli are infiltrated and destroyed by small round cells. B (×450) is from the patient in Case 65, large-cell carcinoma showing leucocytic infiltration, a bad prognostic sign. Calcification, as shown in Fig. 2 *A*, was present in specimen from which *B* was taken. *C* (×120) shows sarcomatous degeneration. Average length of life of the three patients illustrated was less than one year.

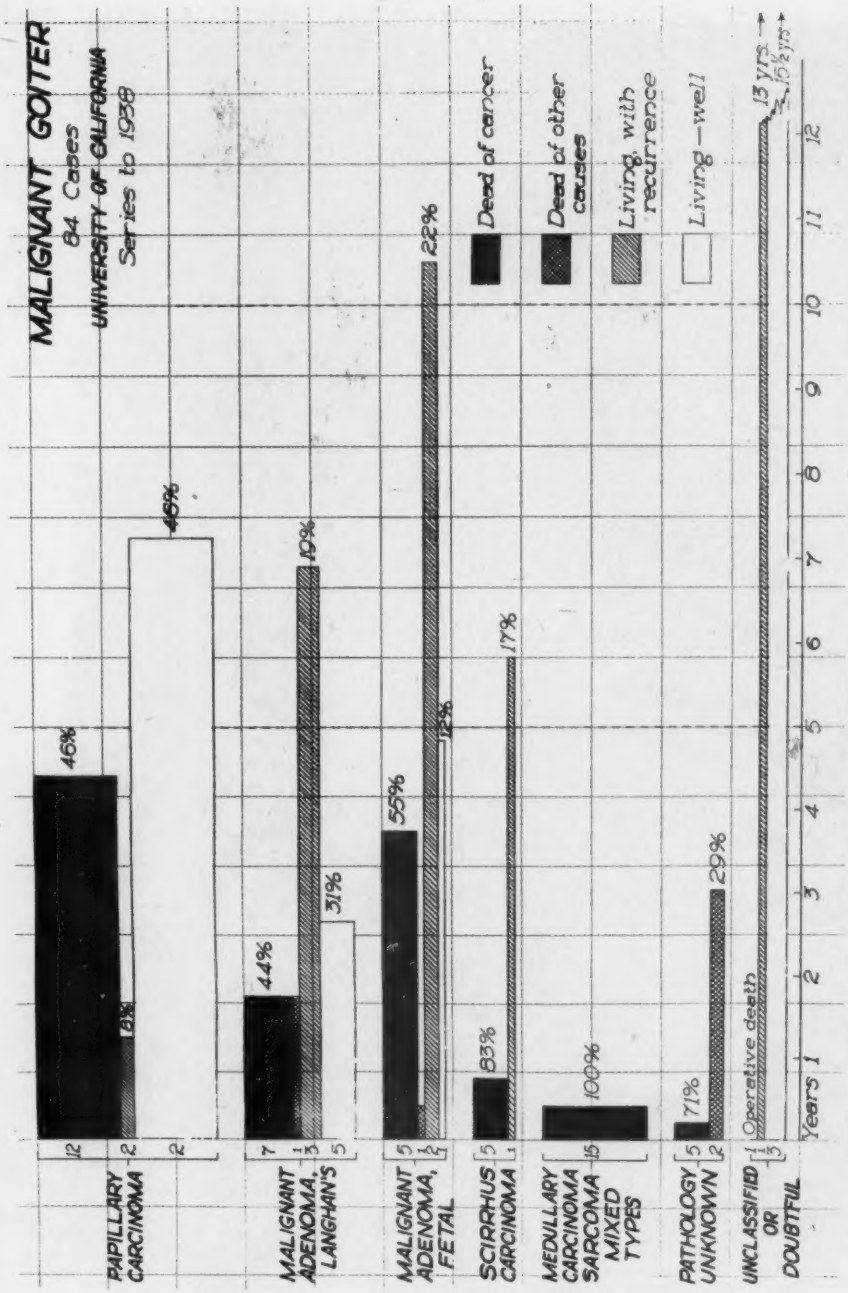
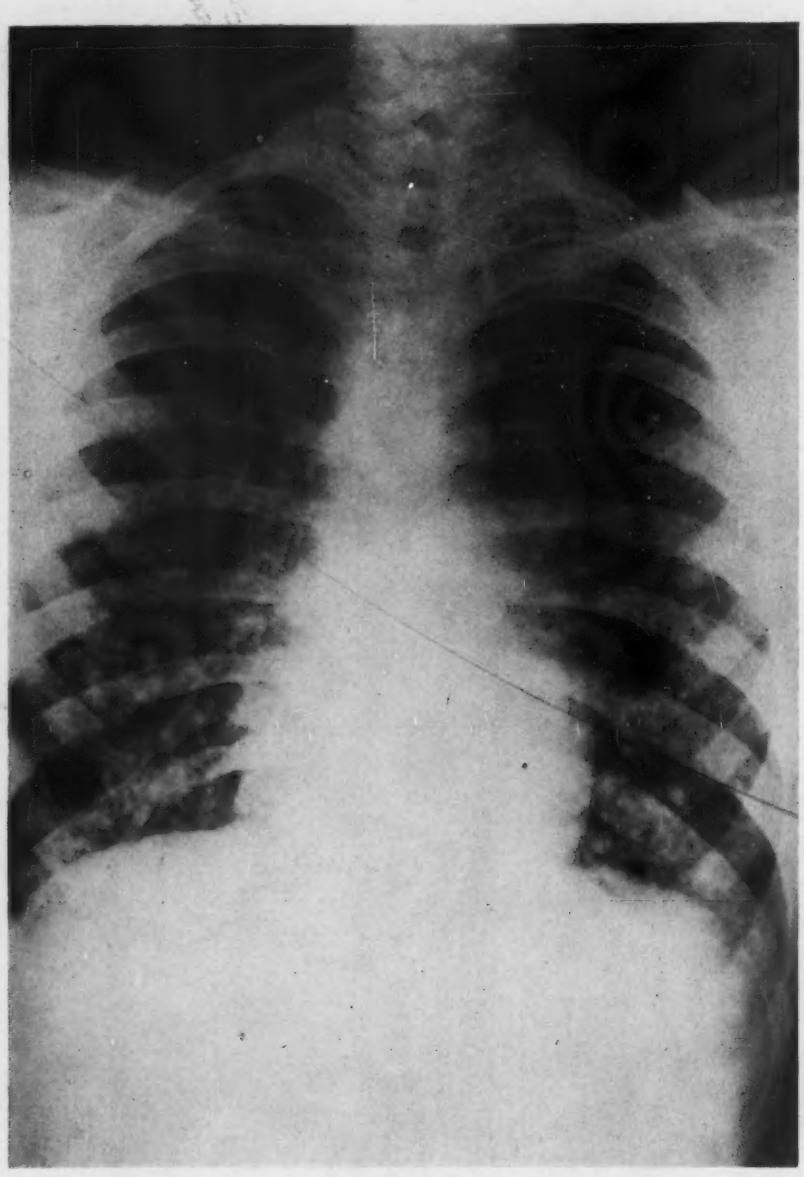


Fig. 6.—Graphic representation of average vital statistics of patients grouped according to pathologic classification of their tumors. Note that there are survivors, apparently well, only in the papillary and malignant adenoma groups.

operation on penetration of the capsule of the adenoma, and diagnosis in the laboratory only on minute gross and microscopic examination of the excised goiter tissue.

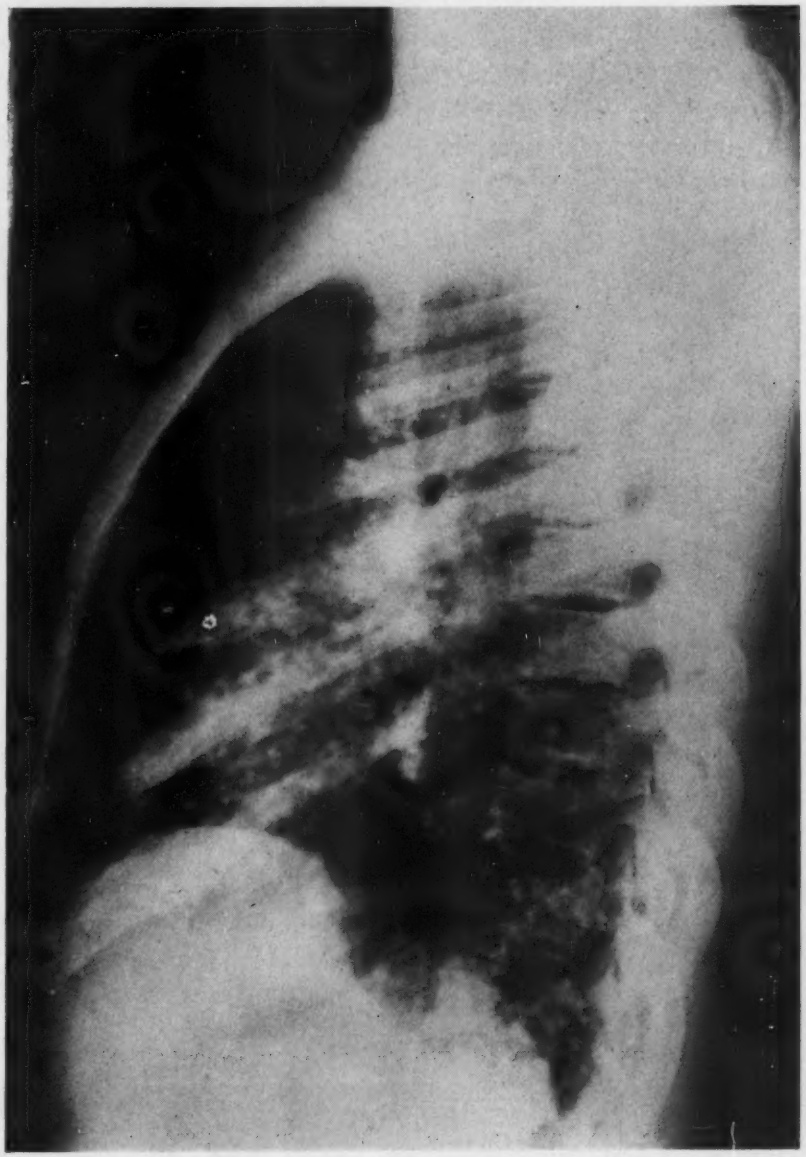


A.

Fig. 7.—Roentgenograms (*A* and *B*) of chest of 9-year-old boy (Case 42) whose chest films show a similar picture now at age 22, and who has developed laryngeal paralysis and local recurrence only recently, thirteen years after operation and irradiation. Microphotograph of tumor from this patient is shown in Fig. 4 *B*.

The second cardinal point in prognosis, the pathologic pattern of the tumor, is well illustrated in the chart shown in Fig. 6. Although this compilation was founded upon eighty-four cases studied to 1938, a similar trend has been shown since that time in double the number of cases

The presence of a papillary pattern is so significant that, as previously indicated,[15] the degree of malignancy apparently can be estimated for a given tumor by the extent of its departure from this pattern; the greater the extent of departure, the more malignant the tumor. The explanation for this phenomenon is twofold: papillary tumors do not tend to



B.

Fig. 7B. *(For legend see opposite page.)*

invade blood vessels, and are thus filtered through the cervical lymphatics; in the series under discussion at least, papillary tumors have been more responsive to irradiation than the more cellular, anaplastic and undifferentiated growths.

The third prognostic point, metastasis, has a value similar to that in malignancy of other organs. The eventual outlook is poor in any case in which distant metastases have taken place. It should be remembered, however, that occasionally metastasis to the lung will lie dormant for many years after removal of the primary tumor. One patient in this series is in apparent good health thirteen years after the lungs were found to be riddled with miliary nodules (Fig. 7). Another has responded well to radiation therapy of pulmonary metastases, and is alive and well three years after operation.

Another feature peculiar to metastasis from the thyroid gland is the not infrequent occurrence of misnamed benign metastasizing goiter.

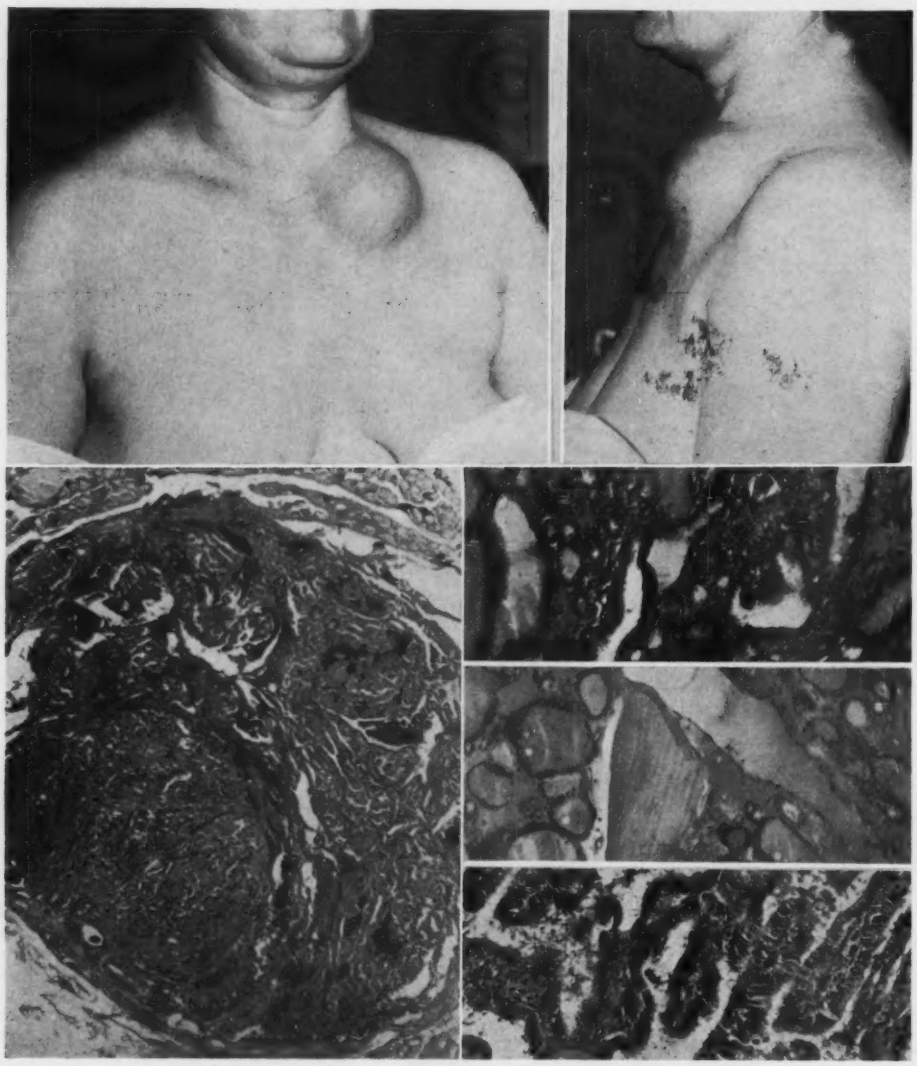


Fig. 8.—Malignant goiter (Case 118), primary lesion of which was discovered only after removal of clavicular tumor had shown it to be of thyroid origin. *A* and *B* show original clavicular tumor: *C* (×30), entire primary tumor of left lobe of thyroid gland; *D* and *E* (×120), sections of growth from clavicle; *F* (×120), section of primary tumor.

The thyroid origin of many metastatic tumors found in bone is recognized only on pathologic examination of the involved section of bone. Like other observers, we have seen a number of these patients who had lived in apparent good health for many years after removal of an isolated metastatic nodule and later thyroidectomy. In some cases the primary lesion is microscopic, and is discovered only by serial section of the entire thyroid gland. Fig. 8 illustrates such a case.

TREATMENT

The discussion of treatment is conveniently divided into three parts, depending upon the stage in which the disease is seen. These stages are prophylactic, definitive, and palliative. Prophylactic treatment consists of the removal of nodular goiters so early that there is no preoperative suspicion of malignant change. For many years surgeons of experience have advocated extirpation of nodular goiters to avoid the danger of malignant degeneration. The statistics in this series (1 carcinoma in 9 men and 1 in 21 women operated on for nodular goiter) amply justify such a plan. This, in my opinion, provides abundant support for the recommendation of an operative procedure which carries as low a mortality and morbidity rate as thyroidectomy. The presence of a solitary adenoma in the thyroid, the finding of lateral masses which could be aberrant thyroid tissue, or the history of onset of rapid growth in a previously quiescent nodular goiter makes such a recommendation urgent. In my experience it has been rare to care for a patient with malignant goiter who has not been told at some time by a physician that the goiter was nontoxic and harmless, and that nothing should be done about it until signs of trouble appeared.

The operation carried out under the heading of prophylaxis varies with the experience of the surgeon and his knowledge of gross pathology. The enucleation of adenomas has been advocated and practiced by surgeons of experience for years. It is a relatively simple procedure, and is highly effective as a prophylactic measure. There have been times, however, when the pathologist has returned a report of malignancy, previously unsuspected, which caused me to regret that I had not performed a lobectomy or a subtotal thyroidectomy. In selected instances of this kind, the surgeon is justified in an immediate reoperation to remove the involved lobe and suspected soft tissue in the neighborhood. There are at least two patients in this series who have remained well for over fifteen years after such a procedure. In one, carcinoma was demonstrated in the specimen removed at the second operation; in the other, none was found.

Any operation for the removal of adenomatous nodules should include a thorough exploration by palpation of the uninvolved lobe, and an exploratory incision into that lobe if any doubt exists concerning the presence of nodules. The operation is incomplete if a single encapsulated nodule is allowed to remain.

If carcinoma is suspected before operation, radical removal of the involved tissue should be planned. A long collar incision should be made, slightly higher than customary. It is occasionally advisable to extend one end of the incision upward, in hockey stick fashion, to facilitate removal of submandibular extensions. The ribbon muscles should always be transected and, if infiltrated by tumor tissue, excised, a procedure which does not militate against a good functional or cosmetic result. The operation should be extensive enough to remove all involved structures and yet preserve at least one recurrent nerve, one parathyroid gland, and both carotid arteries. Crile and Crile[3] described a satisfactory technique for such an operation. If removal necessitates the sacrifice of one recurrent nerve this should be done, provided that preoperative examination showed the other to be functioning. The use of an intratracheal catheter with an inflatable cuff, regardless of the type of anesthesia employed, is of great advantage. This prevents the collapse of a trachea softened by pressure or infiltration, and aids oxygenation during the operation.

When the lateral or inferior veins are found to be thrombosed by tumor tissue, ligation and resection of the internal jugulars should be attempted. Tumor invading the trachea should be excised flush with the tracheal wall either with the scalpel or the electric knife, and the base should be lightly coagulated. Special care must be taken to prevent injury to the esophagus, which may be adherent to the retrotracheal portion of the tumor.

Mediastinal extension of malignant tissue often proves to be the unsurmountable obstacle to complete removal of the tumor. If the growth is hard in consistency and of the infiltrating type, little can be done to excise the substernal portion even by splitting the sternum. If, on the other hand, the mediastinal portion consists of more or less encapsulated nodules, there are two methods of manipulation which may accomplish removal. The first of these is the operation described by Lahey[10] for ablation of substernal adenoma. In this procedure, the suprasternal portions of the tumor are freed from their bed and from the trachea, and are used to pull the mediastinal masses into the neck. The second method can be employed for many of the softer papillary growths and for those in which central degeneration of a nodule permits rupture of the pseudocapsule. In such a case, it may be possible to evacuate the mushy contents by curette or suction and collapse the capsule, thus permitting extracapsular finger dissection from the superior mediastinum.

After removal of the tumor, it is advisable to lavage with plain sterile water instead of saline solution because of the lytic effect of the former on possible free cancer cells. Lavage before closure reveals possible sources of bleeding and removes cellular débris, deposit of which is almost unavoidable in manipulation of the more friable tumors.

RADIATION THERAPY

Roentgen therapy can be used alone for palliation or combined with surgery in an attempt to eradicate the disease. Even in advanced cases, a biopsy should be performed before irradiation is carried out. This offers the dual advantage of establishing the diagnosis and preventing irradiation of a pure papillary tumor, which may break down and ulcerate because of its extreme radiosensitivity. Since treatment of the patient shown in Fig. 9, even large, bulky papillary tumors have been surgically removed, followed by adequate postoperative radiation therapy in the hope of obtaining a cure. This patient died six weeks later of empyema secondary to tearing of the pleural apex at operation. Autopsy examination revealed no malignant tissue.

The principal value of x-ray therapy lies in its administration postoperatively, directed to the elimination of cancerous tissue not detected or not removable at operation. Such tissue is frequently located in the mediastinum, and for this reason the mediastinal space should be included in the area treated. Three thousand roentgens delivered to the tumor bed are considered to be the lower limit of effective dosage. The aim is to administer a dose sufficient to kill cancer cells, but not to exceed the tolerance of normal tissues in the irradiated zone. The best results can be expected to occur in tumors shown to be predominantly papillary in design. This has been substantiated in our series, and in Portmann's[11] studies 92 per cent of patients with papillary carcinoma survived more than five years. Not only are a greater number of apparent cures obtained by combined surgery and irradiation in the papillary group, but when recurrence does take place these tumors are more responsive and remain susceptible to radiation therapy for a longer period of time. It must be remembered, as Haagensen[8] pointed out, that sensitivity to irradiation should be judged from two aspects: the immediate response as shown by regression of the tumor, and the duration of that response. In both these respects, papillary tumors are the most susceptible to irradiation.

Other than for the papillary carcinomas, we have found little evidence that radiation therapy is of value except in a rather small number of malignant adenomas. It is, however, extremely difficult to estimate precisely the value of radiation therapy. When it is employed after operation, and the patient remains well and without recurrence, it is impossible to state whether the favorable result is due to the completeness of operative removal or to irradiation. Only when a tumor recurs and regresses or becomes dormant under a course of radiation therapy can the successful outcome be attributed wholly to this form of treatment. In the papillary group, a fair number of such cases has been followed for many years, a less number in the group comprised of Langhans' malignant adenoma, and very few in the fetal types of malignant adenoma. No case of anaplastic, large and small cell carcinoma, or car-

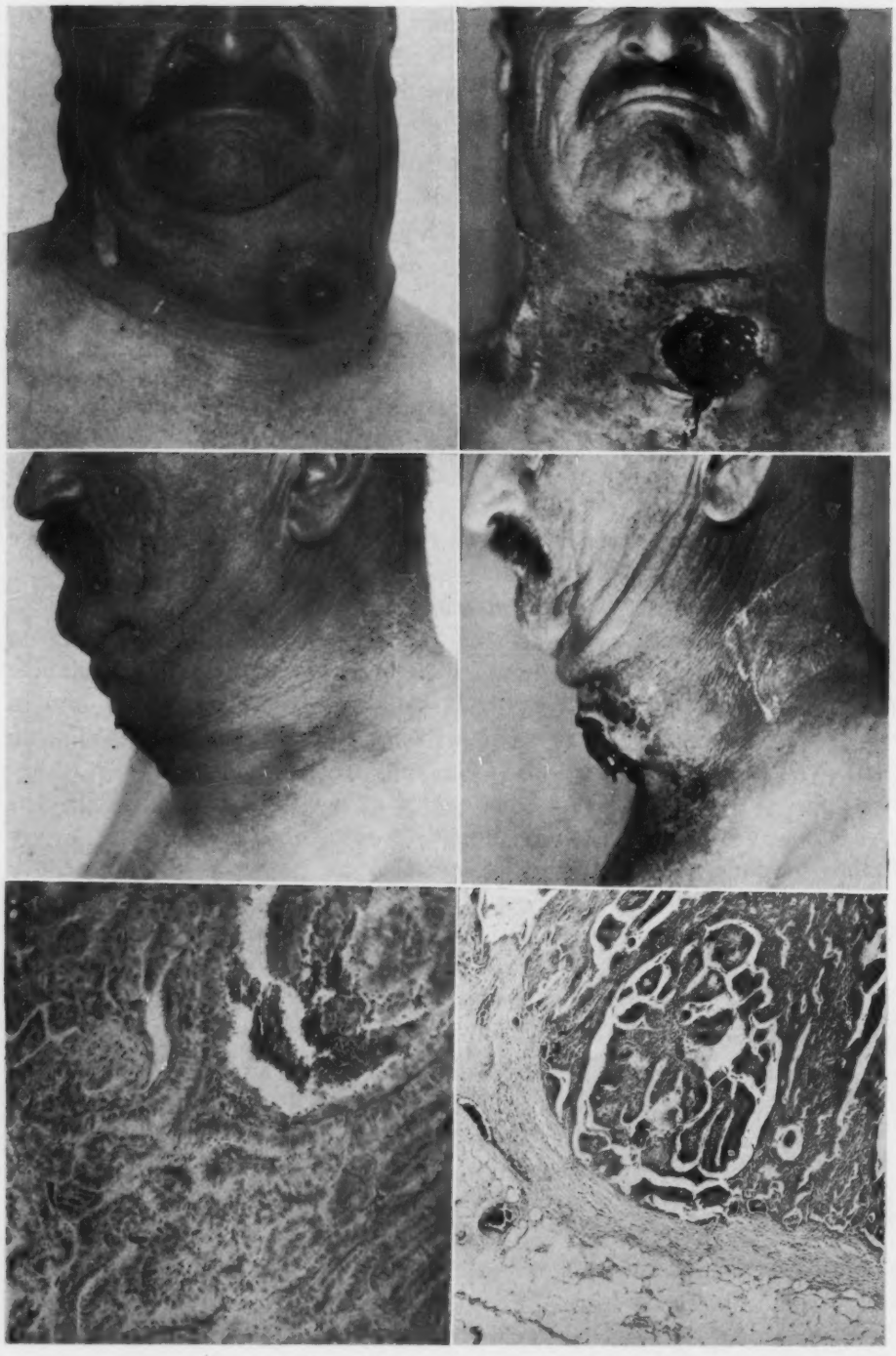


Fig. 9.—Patient (Case 41) before and after radiation therapy. Left column (*A*, *B*, and *C*) including microphotograph (×120), represents condition before roentgen therapy. Right column (*D*, *E*, and *F*), shows condition shortly after completion of treatment; microphotograph (×80).

cinosarcoma has shown a favorable response to surgery or to irradiation (Fig. 6). It should be emphasized that surgery and irradiation are directed toward accomplishment of the same result—eradication of the growth. They are not antagonistic, but complementary, to each other. The most favorable results are to be anticipated when irradiation follows surgery; but occasionally x-ray therapy before operation makes surgical removal possible. In such cases, operation should be followed by adequate roentgen therapy.

TREATMENT OF RECURRENCE AND METASTASIS

The results of treatment of locally recurrent tumors and metastatic deposits are influenced even more strongly by the pathologic pattern of the growth than are the results of treatment of primary neoplasms. If the metastases are from a well-differentiated tumor, especially if it is predominantly papilliferous, their response to irradiation is usually good. If, on the other hand, they are of the usual blood-borne variety, malignant adenoma Langhans, they have in my experience shown little response to radiation therapy. Regardless of the pattern of the parent tumor, it is wise to give the patient a trial of irradiation if the metastatic lesions are not too widespread and fulminating.

Local recurrent nodules, especially if the primary growth was a malignant adenoma, should be removed. Graham[7] demonstrated that many of these cervical masses are tumor thrombi, often encapsulated in the lateral or inferior thyroid veins. Their removal by operation is especially indicated because of their lack of response to irradiation, and because years may intervene before they metastasize or recur again locally.

SUMMARY

1. Almost all malignant goiters are nodular. Carcinoma occurs so rarely in diffuse toxic goiter (1 in 168 malignancies in our series), that this group can be excluded from consideration.

2. The incidence of malignant goiter is influenced by the degree of endemicity and the frequency of nodular goiter in a given geographical locality.

3. Age groups of patients with carcinoma of the thyroid are similar to those of patients affected by this lesion in other organs, except that malignancy appears in aberrant thyroid tissue earlier in life.

4. The preponderance of malignant goiter is in favor of women; but the expectancy for carcinoma in men with nodular goiter is much greater—1 in 9 men (11 per cent) coming to surgery.

5. Of the three cardinal signs of malignant goiter: hoarseness, fixation, and hardness, at least the first two denote a far-advanced lesion. Any or all of these signs, however, can be produced by benign growths. Carcinomatous and calcareous degeneration may occur in the same nodule, and delay in removing it alters the prognosis unfavorably.

6. Long-standing or slowly growing tumors which suddenly undergo rapid growth and produce pressure symptoms are suspicious and should be extirpated before the clinical picture of malignancy develops.

7. We have found it practical from a prognostic and therapeutic standpoint to classify malignant thyroid tumors according to their characteristics of growth and their microscopic architecture. Table II shows our three groups: .papillary carcinomas, malignant adenomas, and all others.

8. Prognosis is based on the time of diagnosis, the pathologic pattern, and the presence of metastasis. Deaths are in direct proportion to the ease of diagnosis. Papillary carcinoma offers the best prognosis, and the degree of malignancy can apparently be estimated by the corresponding extent of departure from the papillary pattern. The prognostic evaluation of metastasis is similar to that in carcinoma of other organs, with the exception of rare dormant metastatic lesions in patients seemingly well years after operation and irradiation.

9. Prophylaxis consists of the removal of nodular goiters so early that there is no preoperative suspicion of malignant change. Our statistics of 1 carcinoma in 9 men and 1 in 21 women operated on for nodular goiter substantiate the importance of this procedure. Suspected or diagnosed carcinoma calls for radical resection, always preserving at least one recurrent nerve, one parathyroid gland, and both carotid arteries.

10. Roentgen therapy can be used alone or in combination with surgery, but should never be administered without the benefit of a biopsy report. Results may be expected to be good in the extremely radiosensitive papillary carcinomas, fair in a small number of malignant adenomas, and unfavorable in all others. The principal value of x-ray therapy lies in its administration postoperatively.

11. Locally recurrent tumors and metastatic deposits are treated depending on their pathologic pattern. Trial irradiation is justified, regardless of the pattern of the primary tumor, if the metastatic lesions are not too widespread and fulminating. Locally recurrent nodules should be surgically removed.

12. Statistics concerning the different types of goiter treated at the University of California Hospital through 1943 are presented, 5,439 cases being reviewed. Of these, 3,539 goiters were nodular, and 168 malignant (4.8 per cent). Living after five years were 20 per cent of the patients in whom carcinoma was diagnosed or suspected before operation, 40 per cent in whom carcinoma was diagnosed at operation, and 80 per cent in whom it was diagnosed first on pathologic examination.

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PARATHYROID TETANY

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IMPROVEMENT in surgical technique has resulted in a steady diminution of the incidence of parathyroid deficiency following operations upon the thyroid gland. The parathyroid glands may be inadvertently removed, or their blood supply may be interfered with by ligation during operation, or by thrombosis or fibrosis occurring later. Tetany from fibrosis usually appears several weeks postoperatively. Occasionally edema in the immediate postoperative period seems to curtail temporarily the blood supply of the parathyroids, for postoperative tetany may be transient, disappearing as the edema subsides.

Despite the fact that modern surgery has reduced its incidence in large clinics to figures ranging from 1.5 to 0.5 per cent,[1] it is likely that the total number of cases has actually increased because of the increasing frequency of operations upon the thyroid and parathyroid glands. Preservation of the posterior thyroid capsule and the principle of subtotal thyroidectomy, with a better understanding of the usual anatomic location and frequent aberration of the four parathyroid glandules, will permit further reduction in postoperative hypoparathyroidism. When a second or third operation is performed the hazards to the parathyroids are, of course, greatly increased. When the parathyroid glands are seriously damaged or removed at operation, tetany may appear within twenty-four hours.

Spontaneous hypoparathyroidism is rare. The clinical state known as idiopathic tetany results, and is similar in all respects to that produced by surgical damage to the glands. Apparently idiopathic tetany was not always so uncommon as it is at present, for large numbers of cases were reported in central Europe toward the end of the last century, particularly in Vienna. In that city between 1880 and 1895 there were 368 cases studied in the General Hospital, the majority of the patients being young cobblers or tailors. The fact that the greatest frequency of onset occurred in the late winter and in these indoor sedentary workers suggests vitamin D deficit as the cause. Infantile tetany or spasmophilia is another condition now seen relatively infrequently. It is apt to occur in babies who have been fed cows' milk instead of human milk. Erdheim believed that it must result from parathyroid insufficiency, since autopsy frequently revealed hemorrhage into these glands. However, in many cases vitamin D deficiency

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and poor calcium intake or absorption seem to play the major role. Here again the incidence is greatest in late winter. In pregnancy and lactation tetany may appear, and may result from a latent hypoparathyroidism which becomes apparent only after there has been a great and prolonged drain upon the maternal calcium stores. Osteomalacia is apt to be present in these women. Similarly, the bone defect known as rickets frequently is present with infantile tetany. It seems likely that in these so-called idiopathic or functional hypoparathyroid states the chain of events may be as follows: first there is a prolonged deficit of vitamin D or of calcium, or both, and in consequence, the parathyroid glands are called upon to secrete an additional amount of hormone to sustain the falling blood calcium. The glands may hypertrophy, and the demand may be successfully met. (Hypertrophy and hyperplasia of the parathyroids are frequent findings in rickets.) If there is an inherent weakness of the glands, or if function eventually fails after prolonged excessive demands, tetany results.

Signs and Symptoms.—When the serum calcium is between 4 and 6 mg. per cent symptoms are usually manifest. Muscular spasm occurs, particularly carpopedal spasm. The facial and abdominal muscles may be thrown into violent contractions by the mildest stimuli. Painful paroxysms may occur spontaneously. Numbness and tingling of face, hands, feet, and legs may be constant. Epileptiform convulsions may occur and in some cases papilledema is present, suggesting intracranial tumor.[2]

When the blood calcium is 7 or 8 mg. per cent the condition is usually latent. Excitement, exertion, overbreathing, or menstruation may provoke an attack. When the tetany is of long duration ectodermal changes occur, the most serious of which is the formation of bilateral cataracts. The hair becomes lifeless and brittle and thins considerably. Nails become ridged, and teeth, especially in growing patients, become ridged and grooved horizontally. Gastrointestinal disturbances are common with abdominal pain, "gas," and alternating constipation and diarrhea. The least pressure on arm or leg may cause cramping. Rapid motion may become impossible without resulting in painful muscular spasm.

Pathologic Physiology.—All true tetany occurs as the result of the presence of insufficient amounts of ionized calcium in the blood. Any condition which decreases the amount of calcium absorbed or which increases the pH of the blood may result in tetany. The total blood calcium may be low, or only the ionized fraction may be subnormal. The effect in either case is to decrease the regulating, inhibitory effect of ionized calcium upon neuromuscular irritability. Phosphate metabolism is closely associated with calcium metabolism and a rise in the blood phosphate is quite regularly accompanied by a fall in the blood calcium, perhaps because there is induced a deposit of calcium and

phosphate in chemical combination. The following clinical forms of tetany have been recognized:

1. Parathyroid insufficiency, postoperative and spontaneous. The parathyroid hormone increases calcium absorption from bone and increases the proportion of ionized calcium in the blood. Hormone lack causes tetany.
2. Calcium starvation: inadequate calcium intake.
3. Poor calcium absorption, occurring with low vitamin D intake, with steatorrhea, and in conditions in which inadequate amounts of bile reach the intestine, calcium soaps being formed and excreted.
4. Calcium depletion: pregnancy, lactation.
5. Alkalosis
   (a) from vomiting, with loss of HCl
   (b) from excessive ingestion of alkaline salts such as sodium bicarbonate
   (c) from overbreathing, with loss of CO_2
6. Excessive phosphate intake, or excessive phosphate retention with hyperphosphatemia, for example, the tetany occurring with "renal rickets."

Diagnosis.—The diagnosis depends upon the recognition of the symptoms and signs, which are usually quite characteristic. Confirmatory evidence may be secured through three signs when the tetany is latent or only manifest at intervals: Erb's, Chvostek's, and Trousseau's signs. Erb's sign consists in the production of muscular contraction with the stimulating electrode over a motor nerve, the response being elicited by a much weaker galvanic electrical stimulus than is normally necessary. The cathodal opening response is obtained with less than 5 ma., while normally over 6 ma. are required. Chvostek's sign consists in a contraction of the innervated muscles in response to gentle tapping over the trunk of the facial nerve just anterior to the external auditory meatus. Trousseau's sign depends upon the temporary deprivation of the blood supply to a nerve trunk, either by direct pressure on the nerve, or by application of a pressure cuff to an extremity. When the blood pressure cuff is applied above the elbow and inflated the typical carpal spasm will occur within one to three minutes. All of these signs depend upon increased irritability of the nerves.

When tetany is due to alkalosis, the total serum calcium level is usually normal. The blood calcium may be low in conditions associated with poor calcium or vitamin D intake or absorption. In hypoparathyroidism the serum calcium may be very low, the lowest levels of 4 to 6 mg. per cent occurring usually in manifest tetany. With levels of 7 or 8 mg. per cent the tetany is apt to be latent. In parathyroid tetany the inorganic phosphate is usually elevated from the

normal of 3 or 4 mg. per cent to 6 or 8 or even 10 mg. per cent. Normal or low blood phosphate may occur in nutritional hypocalcemia. Blood phosphate may rise with severe kidney damage, with consequent fall in the serum calcium and production of tetany.

Treatment.—The proper therapy of tetany will, of course, depend upon its etiology. Correction of alkalosis by prevention of overbreathing, or by ingestion of ammonium chloride or dilute hydrochloric acid may be indicated. Restoration of adequate calcium and vitamin D intake, and measures to promote their absorption, are necessary when the calcium metabolism derangement lies in this sphere.

We are here primarily concerned with parathyroid tetany. Treatment of hypoparathyroidism may be considered under two headings: the acute attack and chronic tetany.

1. *The Acute Attack:* A patient may die in a severe attack, from spasm of the glottis, or of the diaphragm, or from repeated epileptiform convulsions. Prompt and vigorous intervention is necessary. The most effective measures are (and they should be given in this order):

(a) *Intravenous calcium.*—Calcium chloride is the most effective measure because of its high calcium content and its acid, highly ionized state. It is, however, highly irritating to tissues, and will cause necrosis if leakage occurs outside the vein. From 10 to 20 c.c. of a 5 per cent solution will cause abrupt termination of most attacks. Less irritating to tissues is calcium gluconate, which may be given intravenously (or deep intramuscularly into the buttock, if intravenous injection is not feasible) in doses of 10 or 20 c.c. of 10 per cent solution. Although the blood calcium is restored to normal promptly, relief will be only transient in severe tetany. The serum calcium will fall within one to four hours to its previous level as a rule. The intravenous injection may be repeated once or twice if necessary until the effect of the second therapeutic measure becomes evident.

(b) *Parathyroid extract.*—One to three cubic centimeters of parathyroid hormone (100 U.S.P. units per cubic centimeter) should be given intravenously or intramuscularly immediately after the intravenous calcium is administered. The effect upon the serum calcium is evident in a few hours, the peak effect usually occurring in from eight to eighteen hours, while in from twenty to twenty-four hours all effect is lost. Therefore, the hormone will usually be giving a good response just about the time the effect of the one or two intravenous calcium injections is wearing off. To maintain an approximately normal blood calcium in a patient with severe hypoparathyroidism requires daily injections of the extract. This is expensive and unpleasant. Furthermore, a tolerance is usually developed, larger and larger doses are required, and finally little or no response occurs. Maintenance treatment of chronic tetany formerly consisted of high calcium intake plus daily hormone injection, but fortunately better methods have been developed.

Another possible means of supplying hormone is the implantation of parathyroid tissue. In our experience such transplants have been ineffective, even when performed after preliminary culture of the parathyroid tissue in the recipient's serum, as advocated by Stone, Owings, and Gey.[3] Even after the procedure was repeated four times at intervals of some months in one of these cases, no definite results were observed. In one patient only temporary benefit was obtained from a parathyroid transplant obtained from her mother.

2. *Chronic Tetany:* The treatment of chronic tetany should begin as soon as it is evident that the patient cannot maintain a normal serum calcium level. The effective measures are:

(a) *High calcium intake.*—A quart of milk will supply approximately 1 Gm. of calcium daily, and, in addition, from 10 to 15 Gm. of calcium lactate or gluconate are usually advisable. This is best taken as two to four teaspoonfuls well stirred in hot water or milk, distributed throughout the day. It is not necessary to limit phosphorus intake, but a high phosphorus diet is undesirable, which means primarily that meat and protein foods should be eaten only in normal amounts.

(b) *Desiccated thyroid.*—Desiccated thyroid promotes calcium absorption and helps maintain a normal serum calcium when hypothyroidism as well as hypoparathyroidism is present. The dose needed varies from 1 to 3 gr. daily, enough being given to restore the basal metabolic rate to normal.

(c) *Dihydrotachysterol* (Hytakerol, Winthrop*).—Dihydrotachysterol can be taken orally in capsules each containing 0.625 mg., and will maintain serum calcium within normal limits in even the most severe cases of hypoparathyroidism.[4] The dose varies with the severity of the case and with the amount of calcium ingested. With higher doses of calcium, smaller doses of dihydrotachysterol are possible. Among fourteen patients we have studied with severe chronic hypoparathyroidism, the requirement is either one or two capsules daily when between 10 and 15 Gm. of calcium lactate powder are taken. In four of the more severe cases the patients need two capsules and 15 Gm. of calcium lactate per day; four patients require one capsule only with the same calcium intake. Of the remaining six patients, three take one capsule and approximately 15 Gm., and three take one capsule and 10 Gm. Twelve of the patients had postoperative tetany, eleven after thyroid operations, one after removal of a parathyroid tumor. Two had idiopathic hypoparathyroidism.

Enough dihydrotachysterol can be given to raise serum calcium to normal even if calcium intake does not exceed that in the normal diet. The amounts of calcium used in this series of patients have not caused

*The dihydrotachysterol for these studies was furnished by the Medical Research Department of the Winthrop Chemical Company, Inc.

digestive upsets, are not particularly disagreeable, and make the treatment much less expensive. From two to four capsules per day are necessary with a normal calcium intake.

The rise in blood calcium is more rapid if larger doses of dihydrotachysterol are given for the first few days and the maintenance dose is adopted when the serum calcium level approaches normal. A good dosage scheme for a patient with a serum calcium of 6 mg., given 15 Gm. of calcium lactate daily, might be one capsule four times daily the first three days, then two capsules per day until the serum calcium reaches 9 or 10 mg. The dose can be reduced to one capsule if the serum calcium exceeds 10 mg., or in a mild case one capsule every other day may suffice. With this dosage scheme a normal serum calcium should be reached in from seven to ten days. The first rise is often not evident for forty-eight hours. When the drug is stopped, the blood calcium falls slowly over a period of two or three weeks. The advantages of dihydrotachysterol over parathyroid extract in the treatment of chronic parathyroid insufficiency are:

1. The action is more prolonged
2. It is effective when taken orally
3. No tolerance is developed
4. It is less expensive
5. It is stable and retains its potency when kept at ordinary room temperatures

Dihydrotachysterol in excessive amounts can cause hypercalcemia and severe toxic effects. Frequent determinations of the blood calcium are necessary until the maintenance dose is established, then the serum calcium need be measured only every two or three months.

(d) *Vitamin D.*—Various forms of vitamin D are effective in raising serum calcium. Doses of from 150,000 to 400,000 U.S.P. units daily plus a fortified calcium intake of 3 Gm. of calcium chloride (as 25 per cent solution in syrup of glycirrhiza) gave good results in a series of six cases studied by Sevringhaus and St. John.[5]

In comparative studies on eight of the fourteen patients in our series we found that vitamin D_2 (calciferol*) gave results similar to those obtained with dihydrotachysterol. Vitamin D seemed to have less effect in promoting phosphorous excretion. Serum phosphate levels tended to be somewhat higher than with dihydrotachysterol. We employed doses of 100,000 units (two capsules) daily in most of our cases, and found this sufficient if from 5 to 15 Gm. of calcium lactate or gluconate were given. The same dangers of hypercalcemia with cumulative effects must be guarded against with vitamin D as with dihydrotachysterol. When the serum calcium was maintained within normal limits, patients felt equally well with the two drugs.

*In the form of Drisdol (Winthrop) 50,000 U.S.P. units per capsule.

SUMMARY

Spontaneous idiopathic tetany and spasmophilia are relatively rare, while postoperative tetany is less frequent as surgical technique improves.

Acute severe tetany demands immediate recognition and treatment. A patient complaining of numbness, tingling, or cramps after a thyroid or parathyroid operation should have a venipuncture with withdrawal of blood for serum calcium determination, then intravenous calcium should be given, and intramuscular parathyroid extract. Should symptoms of tetany persist for several days, treatment with high calcium intake and dihydrotachysterol or vitamin D should be instituted. Chronic tetany is a severe illness causing much discomfort and disability as well as late trophic changes such as cataracts. Good treatment now relieves patients of all such symptoms and prevents the trophic changes.

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Editorial

Progress and Future in the Treatment of Goiter

TWO or three decades ago a succession of important discoveries in the field of goiter was announced. These included the isolation of thyroxin by Kendall (1914), prevention of goiter with iodine by Marine and Kimball (in the school children of Akron, 1921), the rediscovery of the beneficial effect of iodine in toxic goiter by Plummer (1923), and the production of thyroid hyperplasia by the thyrotropic hormone of the pituitary gland (Loeb and Bassett, 1929). These milestones of progress gave promise of solving the mystery of etiology of goiter and simplifying treatment with perhaps the elimination of surgical procedures; however, these accomplishments were not immediately forthcoming. Although valuable contributions have been made since these discoveries, none could be considered epochal until the inhibiting effect of thiouracil and thiourea was demonstrated by Astwood (1943), following the experimental work of Kennedy and Purves (1941) and others. The primary value of thiouracil, like iodine, is in preparation of the patient for operation. However, preliminary experiences of Astwood on prolonged treatment with thiouracil as reported in this symposium suggest that symptoms may not recur following discontinuance of the drug at least in some of the patients. The effect of thiouracil in neutralizing thyrotoxicosis is much more pronounced than iodine—so much so that postoperative crisis will probably be completely eradicated with its use. However, the relatively slow action of thiouracil may make it uneconomical to use in mildly toxic goiter where iodine preparation is entirely adequate and requires a much shorter period of preoperative therapy. Although the basic cause of toxic goiter remains undiscovered, it is now obvious that the serious aspects of the disease have been almost totally eliminated. The incidence of goiter has decreased in a few localities, at least. The report of Marine and Kimball revealed the efficacy of iodine (in the form of iodized salt) in the prevention of goiter (toxic as well as nontoxic) in school children of Akron. Although this work, with similar results, has been extended by Kimball (1938) in Michigan, the public health aspects have not been appreciated sufficiently for the use of iodized salt or equivalent iodine therapy to be adopted universally. Recently many clinicians have gained the impression that there is a definite decrease in the incidence of toxic goiter presumably based on the use of iodized salt. The writer was not convinced of this decrease in incidence in goiter in adults until recently, when the number of goiter patients was compared

to other admissions to Illinois Research Hospital. Fig. 1 illustrates the percentage of thyroid patients in the total admissions on the surgical service (adults) in Illinois Research Hospital. The average yearly incidence of thyroidectomies for goiter (inclusive of toxic diffuse, toxic nodular, and nontoxic nodular) in the total number of admissions on the surgical service for the three-year period of 1927, 1928, and 1929 was 19.3 per cent, whereas the average for the years 1941, 1942, and 1943 was 11.3 per cent of surgical admissions. During these two periods the number of thyroidectomies comprised 3 per cent and 1.9 per cent, respectively, of the total admissions (all services) to the hospital. This decrease in incidence is too great to be considered a coincidence; the

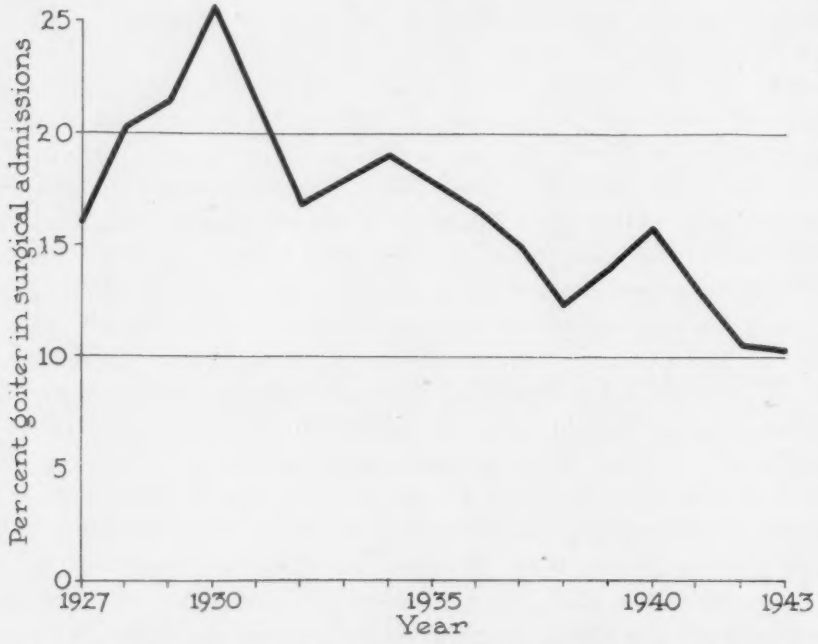

Fig. 1.—The curve illustrates the decline in incidence of goiter (thyroidectomy) in the total surgical admissions to Illinois Research Hospital.

use of iodized salt appears to be the best explanation of this decrease in goiter. The use of iodized salt* in the Chicago area was begun in 1924. Naturally, it would take a few years for the iodine therapy to be reflected in the incidence of goiter. The drop in the incidence of goiter (operations) in the total surgical admissions, from 19.3 per cent to 11.3 per cent in the fourteen-year interval, can be explained better by the factor of increased iodine intake than by any other local factor known to the writer. The amount of iodized salt sold in 1924 after its introduction was estimated at 60 to 65 per cent. Of the total amount sold during the past few years this percentage has decreased slightly, being 58 per cent in 1943. The ratio of the various types of goiter has remained relatively unchanged, indicating that whatever the cause of the decrease in goiter

*Data kindly supplied by the Morton Salt Company, Chicago.

of operable type, the various types have been affected equally. However, it must be emphasized that restoration of the proper iodine intake alone cannot be expected to eliminate goiter because goiter of all types still exists along the seaboard where iodine intake (particularly in drinking water) is presumably adequate. Moreover, the added intake of iodine in iodized salt in these communities during the past few years has not resulted in any decrease in goiter. As a matter of fact, in some communities (for example, New Orleans) the incidence of goiter appears to be on the increase.*

Much difference of opinion exists as to whether or not excision of nontoxic nodular goiter is advisable. However, at least a great many surgeons advise removal because of the possible development of carcinoma, thyrotoxicosis, and pressure manifestations. After reviewing the incidence of carcinoma of the thyroid in nontoxic nodular goiters removed at Illinois Research Hospital, the author became convinced that removal of nontoxic nodular goiter should be advised almost routinely except in aged people or patients with complicating diseases. In general, the urgency is greater in young people, particularly if the nodule is solitary, largely because the incidence of carcinoma is highest in these two instances.

During the past several years the mortality rate following thyroidectomy has been lowered gradually until now it will probably average between 0.5 and 1.5 per cent in the various clinics where a large number of patients are cared for. There will be or should be a definite superiority of mortality rate in a series dealing with private cases over a series in a charity clinic for two reasons: (1) Private patients will come to the physician earlier, that is before cardiac and other organic damage is pronounced; and (2) for financial reasons the nutritional imbalance will be greater in the charity patient—a serious detriment in a disease which affects nutrition primarily. To maintain a commendable mortality rate the surgeon must be particularly cautious in his estimation of operability. This precaution is just as important in thyrotoxicosis as it is in other diseases such as carcinoma of the colon and stomach where nutritional depreciation is such a prominent factor. Although the experienced clinician may estimate operability quite accurately by a brief survey of the patient, he will nevertheless make fewer errors if he will adopt mathematical principles as much as possible; he will certainly have an enormous amount of difficulty in teaching methods of estimating operability to students unless he utilizes mathematical principles in his prerequisites.

Whatever the method adopted for estimating operability, there is one prerequisite which must never be broken, that is, bilateral thyroidectomy must never be performed in severe thyrotoxicosis unless the patient is showing a weight gain. In patients with doubtful operability, only one

*Ochsner, Alton: Personal communication.

lobe should be removed at the first operation. An interval of at least three or four weeks should intervene before the second lobe is removed. Ligation of the superior thyroid artery has been abandoned as a stage operation.

Since thiouracil is so effective in neutralizing toxicity, the need for stage operations will unquestionably be markedly decreased. In spite of this tremendous advantage of thiouracil over iodine, it possesses two disadvantages, (1) the drug is occasionally toxic, and (2) a much longer interval is required to obtain reduction in the thyroid toxicity.

—*Warren H. Cole, M.D.*
Chicago, Ill.

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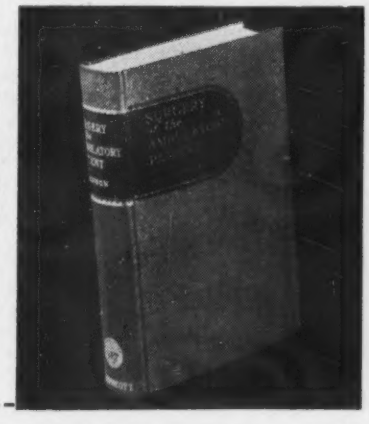
SECTION I *General Discussion:* Equipment, anesthetics, preparation and conduct of operations, post-operative care, dressings and bandages, infections, care of wounds, burns, frostbite and superficial cysts and tumors.

SECTION II *Regional Surgery:* Actual surgery as required by and applied to various body regions. Arrangement of data begins with the scalp and ends with the foot. Covers every known condition of the soft tissues from its ambulatory-surgical aspect.

SECTION III *The Musculoskeletal System:* Complete coverage in the same "head-to-foot" way. The material in this section was written by Dr. Louis Kaplan, Head of the Fracture Division of the Surgical Out-Patient Department, Hospital of the U. of Pennsylvania.



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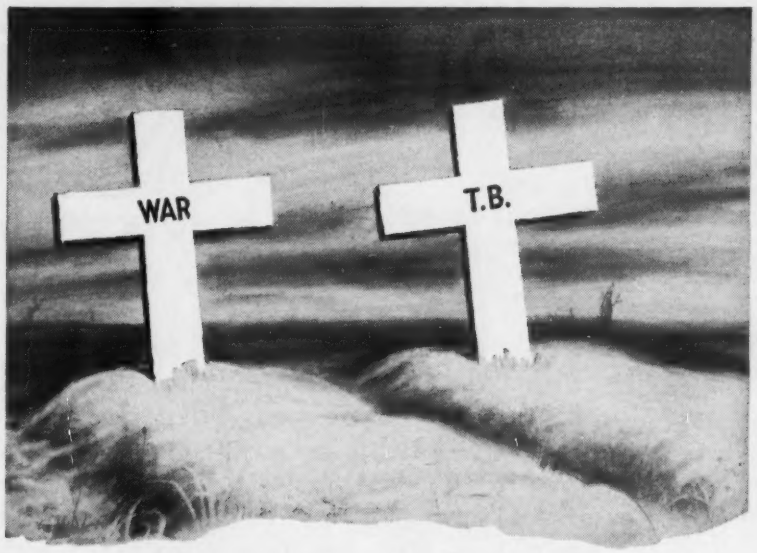

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National, State and Local Tuberculosis Associations in the United States (Christmas Seals) ---------- 19

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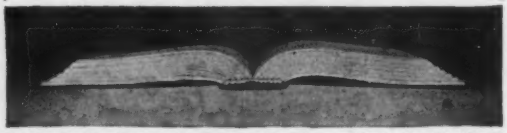

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